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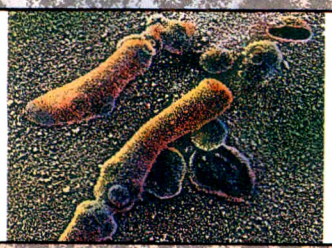
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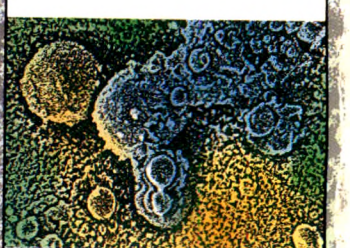
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BEFORE
Scanning electron micrograph (×3300) of *Candida albicans* grown for 48 hours on agar.

Culture

Femstat Prefill destroys the integrity of the yeast cell.



AFTER
Scanning electron micrograph (×3300) of *Candida albicans* on agar plate with butoconazole nitrate.

Shock.

Cure[1]* with 3-day† therapy

■ Microbiological cure rates in 95% of patients eight days following Femstat three-day therapy.[1]

Broad spectrum of activity

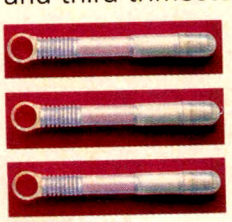
■ Clinically effective against *Candida albicans* and other *Candida* species, including *Candida tropicalis.*

Broad margin of safety

■ A low incidence of reported adverse reactions.[2]

■ NOT a triazole/NOT associated with flu-like symptoms.

■ Proven safe and effective for use in pregnant patients† (second and third trimesters only).



3 prefilled disposable applicators

■ Reduces risk of reinfection and ensures unit-dose accuracy.

■ Eliminates messy filling/cleaning procedures.

1. Droegemueller W, Adamson DG, Brown D, et al: Three-day treatment with butoconazole nitrate for vulvovaginal candidiasis. *Obstet Gynecol* 1984;64(4):530–534. 2. Prescribing information for Femstat® Prefill vaginal cream.
*Microbiological cure rates in 95% of patients eight days following Femstat 3-day therapy.[1] †In pregnant patients (second and third trimesters only), therapy should be extended to six days.
Please see brief summary of prescribing information on page following this advertisement.

FEMSTAT® PREFILL

(butoconazole nitrate) VAGINAL CREAM 2%

3-day† victory over vulvovaginal candidiasis

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FEMSTAT PREFILL

(butoconazole nitrate) VAGINAL CREAM 2%

BRIEF SUMMARY

INDICATIONS: FEMSTAT® (butoconazole nitrate) vaginal cream 2% is indicated for local treatment of vulvovaginal mycotic infections caused by Candida species. Confirm the diagnosis by KOH smears and/or cultures. FEMSTAT can be used with oral contraceptives and antibiotics. It is effective in non-pregnant women and during the second and third trimesters of pregnancy.

CONTRAINDICATIONS: FEMSTAT is contraindicated in patients hypersensitive to any of the ingredients.

PRECAUTIONS: General: If clinical symptoms persist, repeat microbiological tests to rule out other pathogens and confirm the diagnosis. Discontinue drug if sensitization or irritation occurs.

Information for the Patient: Do not discontinue prematurely during menstruation or because of symptomatic relief.

Carcinogenesis: Animal studies have not been done.

Mutagenesis: Mutagenicity studies were negative.

Impairment of Fertility: Animal studies showed no impairment of fertility.

Pregnancy Category C: Adverse effects were noted in animals treated with high oral doses. No studies were done in women during first trimester. Patients in the second or third trimester have shown no adverse effects attributable to the drug.

Nursing Mothers: Use with caution.

Pediatric Use: Safety and efficacy have not been established.

ADVERSE REACTIONS: Vulvar/vaginal burning in 2.3% of patients, vulvar itching in 0.9%, discharge, soreness, swelling, itching of fingers each in 0.2%. Complaints caused 1.6% to discontinue drug.

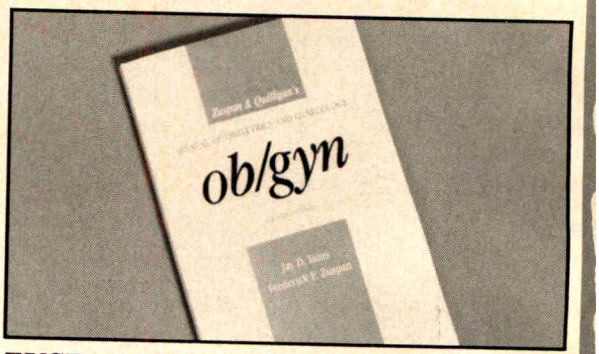
DOSAGE AND ADMINISTRATION: Non-pregnant Patients: The recommended dose is one applicatorful of cream (approximately 5 grams) intravaginally at bedtime for three days. Treatment can be extended for an additional three days if necessary.

Pregnant Patients (second and third trimesters only): The recommended dose is one applicatorful of cream (approximately 5 grams) intravaginally at bedtime for six days.

CAUTION:
Federal law prohibits dispensing without prescription.

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Indications and Usage — TRIPHASIL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications — OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thrombo-embolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners pre-scribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems* — An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS — In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI) — An increased risk of MI associated with the use of OC's has been reported, con-firming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE — In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES — A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34 — 5/100,000; ages 35-44 — 33/100,000; ages 45-49 — 140/100,000), risk being concentrated in older women, in those with long duration of use and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS — Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained elevated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI persisted for at least 9 years in women 40 to 49 years old who had used OC's for 5 or more years. Findings in both studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions* — There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma* — Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic mea-sures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors* — Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring* — Use of female sex hormones — both estrogenic and progestational agents — during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease* — Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects* — Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increases in triglycerides and total phospholipids have been observed in patients on OC's. Three studies were performed with Triphasil and no significant alterations in lipid metabolism were noted except for a slight increase in triglyceride levels in 1 study. Clinical significance of these findings remains to be defined.

8. *Elevated Blood Pressure* — Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache* — Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities* — Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy* — Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding* — OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions — GENERAL — 1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination and Pap smear. 2. Under influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related. 4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution. 7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined. 8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of OC therapy when relevant specimens are submitted. 10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's. a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient — See Patient Package Labeling.

Drug Interactions — Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis — See Warnings section for information on carcinogenesis.

Pregnancy — Category X. See Contraindications, Warnings.

Nursing Mothers — See Warnings.

Adverse Reactions — An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses. The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, hemolytic uremic syndrome.

Acute Overdose — Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration — For maximum contraceptive effectiveness, Triphasil must be taken exactly as directed and at intervals not over 24 hours. (If Triphasil is first taken later than first day of first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on it until after the first 7 consecutive days of use. Possibility of ovulation and conception prior to initiation of medication should be considered.)

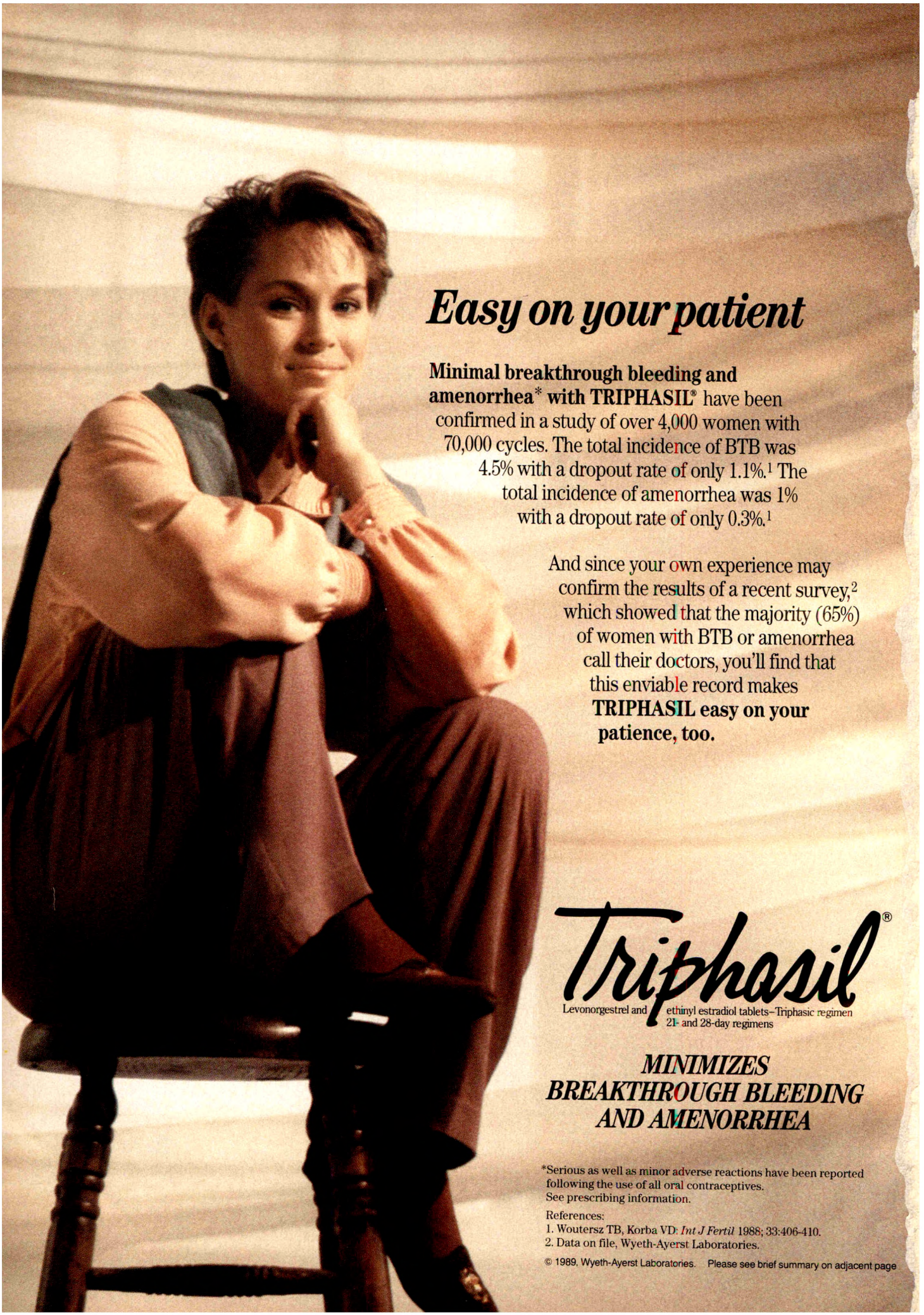
Any time patient misses 1 or 2 brown, white or light-yellow tablets, she should also use another contraceptive method until she has taken a tablet daily for 7 consecutive days.

For full details on dosage and administration see prescribing information in package insert.

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And since your own experience may confirm the results of a recent survey,[2] which showed that the majority (65%) of women with BTB or amenorrhea call their doctors, you'll find that this enviable record makes **TRIPHASIL easy on your patience, too.**

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21- and 28-day regimens

MINIMIZES BREAKTHROUGH BLEEDING AND AMENORRHEA

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives.
See prescribing information.

References:
1. Woutersz TB, Korba VD: *Int J Fertil* 1988; 33:406-410.
2. Data on file, Wyeth-Ayerst Laboratories.

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Mosby Year Book

American Journal of Obstetrics and Gynecology

Founded in 1920

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June
1990

This issue contains Transactions of the Fifty-sixth Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society and Transactions of the Fifty-seventh Annual Meeting of the Central Association of Obstetricians and Gynecologists beginning on page 1499.

TRANSACTIONS OF THE FIFTY-SIXTH ANNUAL MEETING OF THE PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The tyranny of technology 1365
David C. Figge, MD
Seattle, Washington

Prophylactic intrapartum amnioinfusion: A randomized clinical trial 1370
Thomas H. Strong, Jr., MD, Gretchen Hetzler, MD, Albert P. Sarno, MD, MAJ, USA, and Richard H. Paul, MD
Los Angeles, California

Amnioinfusion in laboring gravid women with oligohydramnios at ≥37 weeks' gestation significantly reduced the incidence of intrapartum morbidity as a result of fetal distress.

Ultrasonography-guided early amniocentesis in singleton pregnancies 1376
Frederick W. Hanson, MD, Regina L. Happ, MD, Frances R. Tennant, PhD, Stacy Hune, MS, and Ann G. Peterson, RN, MN
Davis, California

A total of 527 early amniocenteses were performed with an overall loss rate of 2.3%, of which 0.8% were probably related to the procedure.

Seventy-one quadruplet pregnancies: Management and outcome 1384
Michael S. Collins, MD, and Janet A. Bleyl, BA
Portland, Oregon, and Stockton, California

The epidemiology, management, and outcome of 71 quadruplet pregnancies that occurred between 1980 and 1989 are characterized.

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John A. Goodno, Jr., MD
Arcadia, California

A 32% incidence of nonpalpable breast cancers was found in a review of 669 breast biopsies performed in Arcadia, California, during 1987 and 1988.

Vaginal birth after cesarean or repeat cesarean section: Medical risks or social realities? 1398
E. Paul Kirk, MD, Kathleen A. Doyle, MD, Janet Leigh, MD, and Mary L. Garrard, MSN
Portland, Oregon

A woman's choice of vaginal birth after cesarean section or elective repeat cesarean may involve social factors more than medical indications.

Stage IA_2 squamous carcinoma of the cervix: Difficult diagnosis and therapeutic dilemma 1406
Benjamin E. Greer, MD, David C. Figge, MD, Hisham K. Tamimi, MD, Joanna M. Cain, MD, and Roger B. Lee, MD
Seattle, Washington

The definition of stage IA_2 was tested by a retrospective review of 50 patients with early invasive squamous cell carcinoma of the cervix treated with radical surgery preceded by conization of the cervix.

Shirodkar cerclage in a multifactorial approach to the patient with advanced cervical changes 1412
Miles J. Novy, MD, Janice Haymond, MD, and Mark Nichols, MD
Portland and Beaverton, Oregon

Shirodkar cerclage with perioperative tocolysis, broad-spectrum antibiotics, and indomethacin was successfully used in patients with advanced cervical changes between 21 and 26 weeks' gestation.

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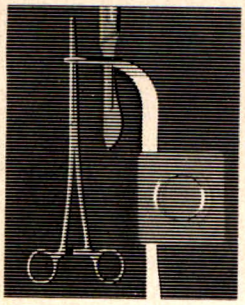
(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, Briceland LL, Cooper B. The conversion of cefoxitin usage to cefotetan: an interdisciplinary approach. *Am J Surg.* 1988; 155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT. Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg.* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference.* ed 43. Oradell, NJ: Medical Economics Co; 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH. Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg.* April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, Outman WR, Deckers PJ, Martens MG. Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg.* 1988;155(5A):67-70. **7.** Centers for Disease Control. 1989 Sexually Transmitted Diseases Treatment Guidelines. *MMWR.* 1989;38(suppl S-8):1-43.

Please see adjacent page for brief summary of prescribing information.

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In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus.**
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.
NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.
INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.
DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.
USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.
IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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J. T. Parer, MD, PhD, and E. G. Livingston, MD
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Richard A. Bashore, MD, William H. Phillips, Jr., MD, and Charles R. Brinkman III, MD
Los Angeles, California

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Neonatal and maternal outcome in low-pelvic and midpelvic operative deliveries 1436
Patricia A. Robertson, MD, Russell K. Laros, Jr., MD, and Rei-Ling Zhao, MD
San Francisco, California

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Kurt Benirschke, MD
San Diego, California

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Joseph W. Hanss, Jr., MD
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John B. Schlaerth, MD, C. Paul Morrow, MD, and Maria Rodriguez, RN
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William E. Crisp, MD, Brian L. Craine, MD, PhD, and Eric A. Craine, PhD
Phoenix and Tucson, Arizona, Oakland, California, and Ft. Collins, Colorado

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Colorado Springs, Colorado

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Mark D. Pearlman, MD, Judith E. Tintinalli, MD, and Robert P. Lorenz, MD
Royal Oak and Detroit, Michigan

The complications of trauma during pregnancy are often predictable and include frequent fetomaternal transfusion, abruptio placentae, and preterm uterine contractions.

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THE PERMANENTE MEDICAL GROUP

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Stockton — Small four physician department in a new clinic building with new equipment, including laser. Stockton's lifestyle is affordable and attractive, offering recreational activities such as boating on the inland waterways. Centrally located, with mountains to the east and San Francisco Bay Area to the west.

Roseville — Eight physicians and two nurse practitioners in clinic setting. Patients are hospitalized for delivery and surgery in Sacramento where physicians take call for L&D and emergency about 5 times each month.

San Francisco — Full range of services including large high-risk, tertiary care OB service. Eighteen physicians, including GYN Oncologist. Residency program. Clinical research and academic teaching appointments available.

Sacramento — Growing metropolitan area between San Francisco Bay Area and Sierra Nevada mountains. Up-to-date facility with active staff of 14 and excellent residency program affiliated with the University of California at Davis. Flexible call averaging five shifts per month covers L&D, emergency room and inpatient services.

Pleasanton — Staffed by four physicians and three nurse practitioners, clinic provides general OB/GYN services, non-stress tests, ultrasound and cystoscopy. Consultant support, including a Perinatologist, readily available. Share call with staff of Walnut Creek Medical Center. Affiliated with the University of California at San Francisco as clinical instructors.

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Dinesh M. Shah, MD, Periclis Roussis, MD, Janet Ulm, MSSW, Phillipe Jeanty, MD, and Frank H. Boehm, MD
Nashville, Tennessee

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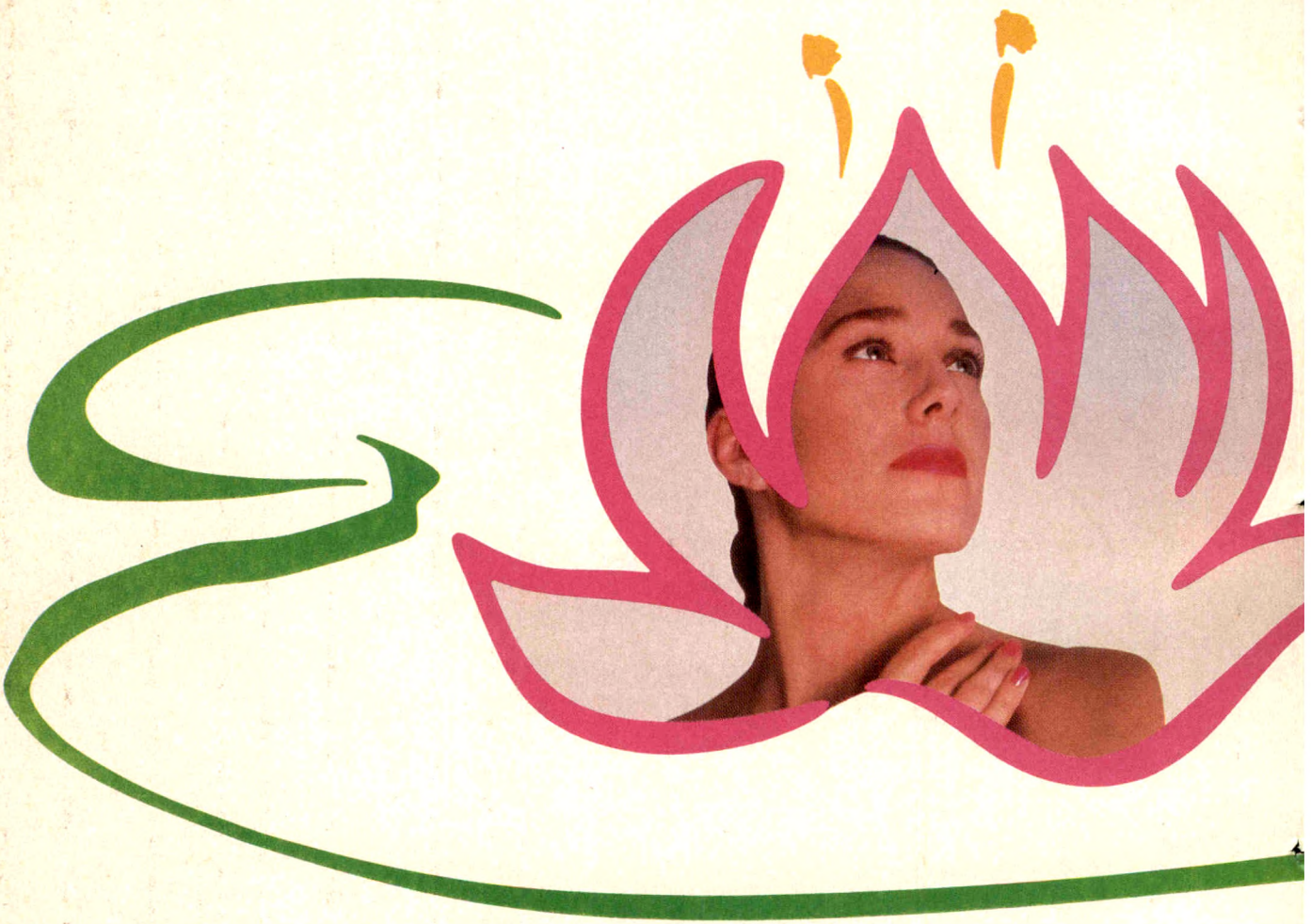
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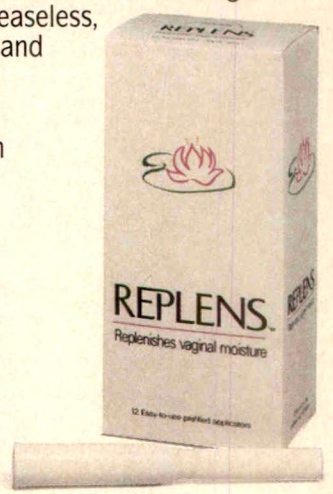
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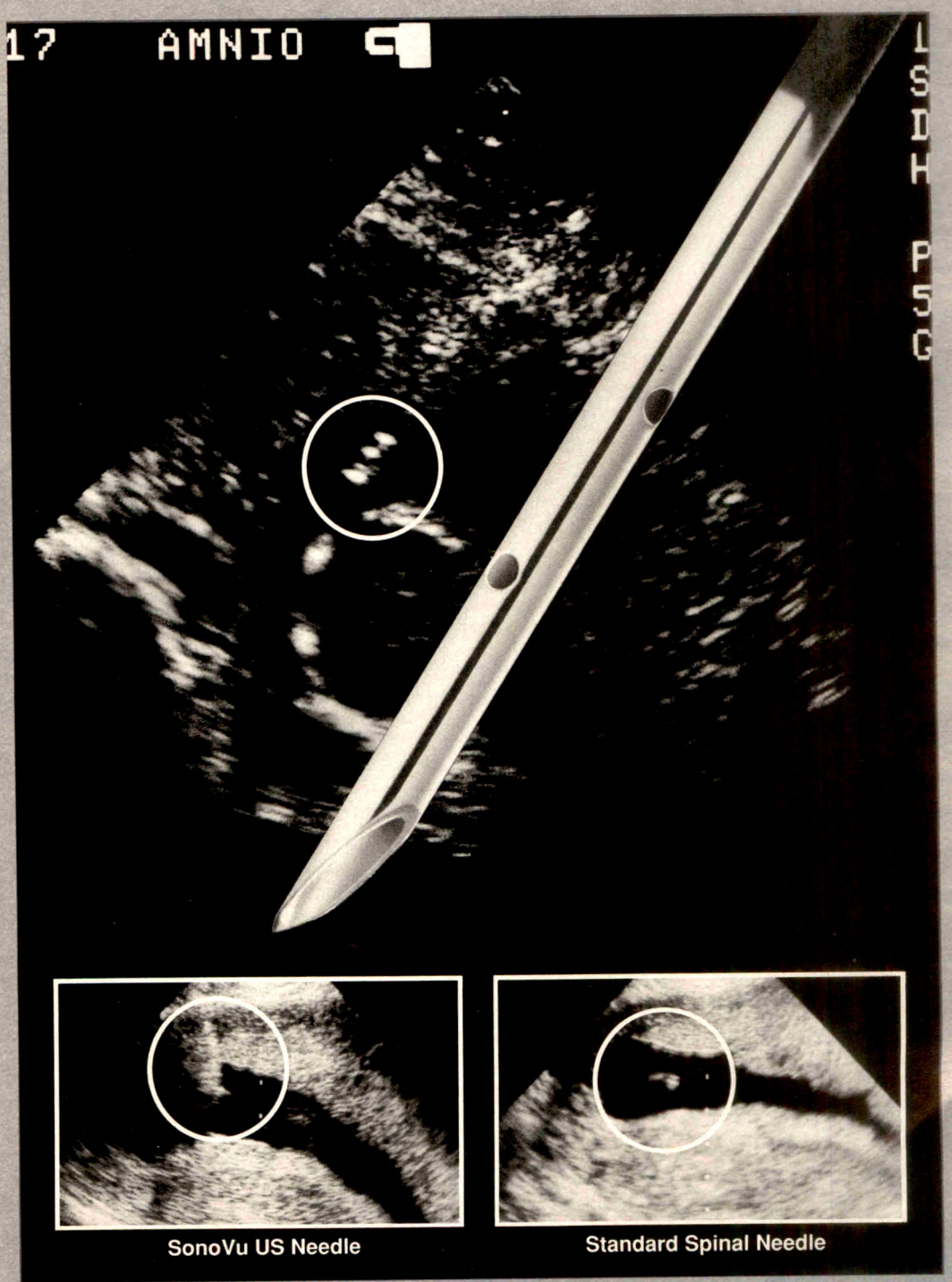
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BOOKS: James VHT, Folkerd EJ, Bonney RC, Beranek PA, Reed MJ. Factors influencing estrogen production and metabolism in postmenopausal women with endocrine cancer. In: van Herendael HB, Riphagen FE, Goessens L, van der Pas H, eds. The climacteric, an update. Lancaster, England: MTP Press, 1983:29.

Personal communications and unpublished data, if essential, may be used but not as numbered references. If they are used, they are to be referred to, within parentheses, at the appropriate location in the text. If used, the author(s) must obtain written and signed permission for their use from the individual being quoted. This signed permission must accompany the manuscript when it is submitted to the Editor. Abstracts are not acceptable as numbered references.

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Do not use paper clips or mar the surface of prints in any way.

Figures must be cited consecutively in the text in Arabic numerals and identified thusly on the back of the print (gummed label with): author(s) name(s), title of article, number, and top marked clearly.

Figures will be returned only on request by the author.

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General

—The original and two copies of the manuscript are submitted.
—The appropriate signed completed checklist and assignment of copyright signed by **all** authors accompany the manuscript.
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—Human experimentation has been approved by the local institution as stated in the Methods section.
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—The covering letter with essential information is with the manuscript.
—All elements of the manuscript are typed double-spaced on bond paper with 1-inch margins at top, bottom, and sides.
—All pages are numbered in the following order: title page, condensation, abstract, body of the text, acknowledgments only of persons who have made substantive contributions to the study, references, legends, and tables.
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BRIEF SUMMARY

TRI-NORINYL® 21-Day Tablets (7 blue tablets of norethindrone 0.5 mg with ethinyl estradiol 0.035 mg, 9 yellow-green tablets of norethindrone 1.0 mg with ethinyl estradiol 0.035 mg, 5 blue tablets of norethindrone 0.5 mg with ethinyl estradiol 0.035 mg)
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BREVICON® 21-Day Tablets (norethindrone 0.5 mg with ethinyl estradiol 0.035 mg)
BREVICON® 28-Day Tablets (21 norethindrone 0.5 mg with ethinyl estradiol 0.035 mg tablets followed by 7 inert tablets)
NORINYL® 1 + 35 21-Day Tablets (norethindrone 1 mg with ethinyl estradiol 0.035 mg)
NORINYL® 1 + 35 28-Day Tablets (21 norethindrone 1 mg with ethinyl estradiol 0.035 mg tablets followed by 7 inert tablets)
NORINYL® 1 + 50 21-Day Tablets (norethindrone 1 mg with mestranol 0.05 mg)
NORINYL® 1 + 50 28-Day Tablets (21 norethindrone 1 mg with mestranol 0.05 mg tablets followed by 7 inert tablets)
NOR-Q.D.® (norethindrone) Tablets 0.35 mg
ORAL CONTRACEPTIVE (O.C.) AGENTS

Indications: Prevention of pregnancy.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who have the following conditions:
- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium, and known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas, carcinomas or benign liver tumors
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, hypercholesterolemia, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations containing 0.05 mg or higher of estrogen. The effects of long term use with lower dose formulations of both estrogens and progestogens remain to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease. Relative risk, the *ratio* of the incidence of a disease among oral contraceptive users to that among non-users cannot be assessed directly from case control studies, but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6. The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women 35 or older, with smoking accounting for the majority of excess cases.

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors for coronary artery disease, such as hypertension, diabetes, hyperlipidemias, hypercholesterolemia, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and impair oral glucose tolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see **WARNINGS,** section 9). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. One cohort study has shown the relative risk to be somewhat lower, about 3 for new cases (subjects with no past history of venous thrombosis or varicose veins) and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A 2- to 6-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery and during and following prolonged immobilization. Since the immediate postpartum period also is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular diseases

An increase in both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. In general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users for both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk also is greater in women 35 or older and among smokers.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with some progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content that produces satisfactory results for the individual.

e. Persistence of risk of vascular disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. Subarachnoid hemorrhage also has a significantly increased relative risk after termination of use of oral contraceptives. However, these studies were performed with oral contraceptive formulations containing 0.05 mg or higher of estrogen.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. However, smokers 35 and older and non-smokers 40 and older who use oral contraceptives have an increase in mortality greater than those using other methods of birth control. These facts must be weighed in conjunction with failure rates for other methods and the risk associated with subsequent pregnancy.

3. CARCINOMA OF THE BREAST AND REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone study also showed no latent effect on the risk of breast cancer for at least a decade following long term use. A few studies have shown a slightly increased relative risk of developing breast cancer, although the methodology of these studies, which included differences in examination of users and non-users and differences in age at start of use, has been questioned.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast or cervical cancers, a cause and effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is less than 1 per 1,000,000 users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. More recent studies do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to impair oral glucose tolerance. Oral contraceptives containing greater than 0.075 mg of estrogen cause glucose intolerance with impaired insulin secretion, while lower doses of estrogen may produce less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS,** sections 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives. The incidence of risk also was reported to increase with continued use and among older women. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. PHYSICAL EXAMINATION AND FOLLOW-UP

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines.

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. CARCINOGENESIS

See **WARNINGS** section.

10. PREGNANCY

Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

INFORMATION FOR THE PATIENT

See **PATIENT LABELING.**

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section):

• Thrombophlebitis • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas, carcinomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

• Mesenteric thrombosis • Retinal thrombosis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

• Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema • Melasma which may persist • Breast changes: tenderness, enlargement, secretion • Change in weight (increase or decrease) • Change in cervical erosion and secretion • Diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine • Rash (allergic) • Mental depression • Reduced tolerance to carbohydrates • Vaginal candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

• Pre-menstrual syndrome • Cataracts • Changes in appetite • Cystitis-like syndrome • Headache • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Vaginitis • Porphyria • Impaired renal function • Hemolytic uremic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis

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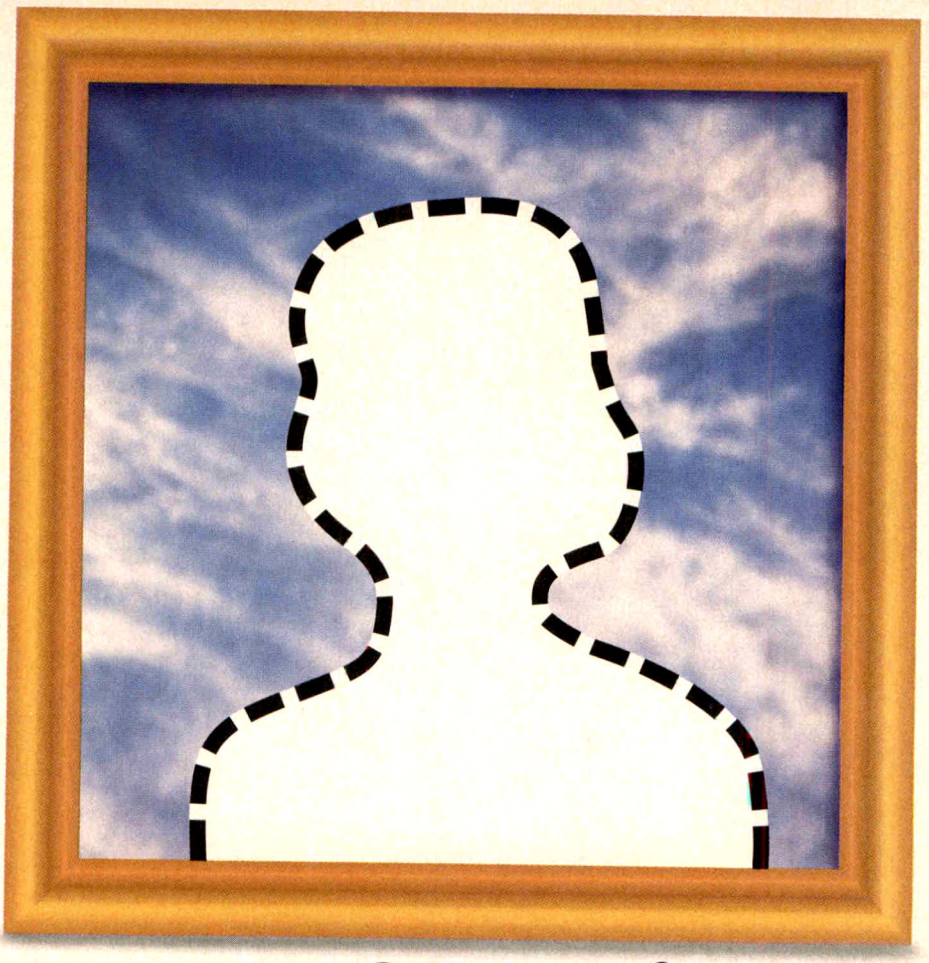
• Decreased incidence of functional ovarian cysts • Decreased incidence of ectopic pregnancies

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The tyranny of technology

Presidential address

David C. Figge, MD

Seattle, Washington

Society's fascination with medical advances, and particularly with the changing technology that highlights those advances, is readily apparent. A sense of drama and expectation seems to surround them and in turn draws the interest of the media. It is this proliferation of medical technology, emerging as it does as the most visible accomplishment of our current generation in medicine, that serves as the subject for my comments today. It is a phenomenon that has dramatically altered the practice of medicine within our specialty. I propose to consider the impact of this developing technology on our society, our educational mission, and finally on the individual practice within our specialty. I will likely reveal some personal prejudices because I must confess a pervasive sense of uneasiness that has come about with my consideration of these changes.

Technology, of course, is merely the application of scientific discovery. It has been suggested that advances in medical technology over the past 20 years alone far exceed those of the previous 200 years. They differ greatly in terms of purpose. Many are diagnostic, such as multichannel chemistry panels, ultrasonography, computerized tomography, electronic fetal monitoring, and nuclear magnetic resonance. Others deal with survival—the evolution of intensive care units. Many, such as renal dialysis and cardiac pacemakers, serve to manage recognized illness. Some, such as organ transplants and joint replacements, actually effect cure and others, such as vaccines, deal with disease prevention. Each category has served to alter the profile of medicine and the impact in the field of obstetrics and gynecology has been particularly striking.

Ultrasonography developed into a medical tool early in the 1970s. The subsequent evolution of gray-scale technology allowed visualization of the internal echo textures. With the introduction of computers into the image-making process, resolution close to 1 mm became possible and enhancement with the vaginal probe allowed measurements of growth in the human follicle. It is now a routine practice to retrieve the ovum at an appropriate time for in vitro fertilization. Its use has been effective in the definition of pelvic neoplasms and in the detection of ascites, hydronephrosis, and metastatic disease. The internal composition of ovarian tumors can be predicted with confidence. Perinatologists and reproductive endocrinologists now regard the availability of ultrasonography as critical within their specialties and refer to ultrasonography as the physician's "third eye." They see it as a tool well within the province of the clinician rather than a facet of diagnostic radiology.

Computed tomography (CT) came about with the development of computer technology. Axial sections at 10 mm intervals are now available in all organ systems. In oncology it has proved particularly helpful in the definition of pelvic side wall disease and in the detection of enlarged paraaortic lymph nodes. Both ultrasonography and the CT scan have permitted accurate aspirations of cells from suspicious intraabdominal masses or nodes with guided thin-needle orientation.

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Magnetic resonance imaging (MRI) closely followed other imaging techniques and has improved on our ability to detect and define intraabdominal pathologic conditions in a noninvasive approach. The leading promise is the hope of distinguishing between inflammatory and neoplastic changes.

The list of achievements is lengthy. Laparoscopy, amniocentesis for prenatal diagnosis, fetal monitoring, laser surgery, villous sampling, and measurements of tumor-specific antigens are all advances within our own time frame. Our specialty in particular has eagerly embraced these technologies and accepted them as inherent tools of clinical practice. Such advances have enhanced our clinical skills and added new dimensions in clinical diagnosis and therapy. We can point to many examples in which the patient has benefitted. It is rewarding to see a woman with an early diagnosis of ectopic pregnancy treated on an ambulatory basis with the distended tube meticulously incised and the aberrant gestation extracted under laparoscopic control. Laser photovaporization guided by the colposcope substitutes for the scalpel in the treatment of intraepithelial neoplasms of the vulva and vagina. Infertile couples may avail themselves of in vitro fertilization. Patients can frequently be managed on an ambulatory basis for disorders that previously required extended hospitalization.

Lay magazines and the popular press have been quick to applaud these new techniques. The ever-scrutinizing legal profession has been quick to recognize them as documentable criteria on which to base decisions of standards in practice. There has been an almost irresistible urge to quickly appropriate each new development into our day-to-day practice. The referring physician can point with pride to the fact that he has already obtained a sonogram and MRI on his patient with uterine cancer. Certainly he is abreast of the current technology! The pressure is compounded by the attitude of an informed public, exposed to glowing reports in the lay literature, who perceives the technology as the "cutting edge" of medicine. Any reluctance on the part of their physician to request this state-of-the-art technology may be regarded as neglect or lack of current medical update.

Like the mythical Roman god Janus, technology projects two faces. Our love affair with technology, interdigitating it into the every fabric of medical care, has also exacted a price—a price often subtle and concealed but nevertheless pervasive. The cost of our emerging technology has generally been ignored or subordinated to the enthusiasms for a new approach. Imaging studies are expensive diagnostic refinements and even ultrasonography carries a significant price tag that should at least allow us to challenge the prevailing tendency to offer it as a substitute for a bimanual pelvic examination. The expense inherent in expensive new technology not only collides with harsh economic realities but in our societal matrix of third-party payments and political expediency it may now have been permitted to grow to a point where it could very well threaten society's economic balance.

In the April 1989 *ACOG Newsletter* the Executive Director of the American College of Obstetricians and Gynecologists, Dr. Warren Pearse, drew our attention to Professor Uwe Reinhardt's observation that there are two alternatives for the regulation of medical costs.[1] Either the total number of dollars paid for medical care can be determined by society, hence allowing physicians to practice as they choose as in the case in the United Kingdom and in some health maintenance organizations *or* the dollars paid may be open ended with regulation of physician services and practice activities. It now appears that the latter option is emerging within this country and will continue if the present indifferent posture over medical costs continues to prevail. We cannot continue to have it both ways and current economics suggest that our window of opportunity is fading.

In 1950 U.S. health care expenditures were $12.7 billion and each American spent $82 per year for this purpose. In 1975 the cost had risen to $132.7 billion and represented 8.4% of our gross national product. By 1985 the figure had risen to $425 billion—10.7% of the gross national product with a per capita expense of $1721—the highest national per capita health expenditure in the world. Health care costs last year (1988) were $618 billion and recent studies project the cost at $1.9 trillion by the year 2000.[2] By 1971 health care costs had exceeded expenditures for national defense and the gap continues to increase.[3] In 33 years health care expenditures in this country as a fraction of the gross national product have more than doubled. A total of 10% of the cost of each medium-sized car goes to pay for health care benefits. Every family must now "tithe" more than 10% of its income to pay for our health care system.[4]

Unlike most economic models, the cost of health care expands without any visible braking mechanism. The consumer and provider both perceive biomedical technologies as desirable and press for their inclusion. These views have been skillfully reinforced by the biomedical science establishment and medical technology industries. With the use of just a few of the most recently developed medical interventions for each individual in our society where it could be indicated could easily absorb the entire gross national product. The costs are eminently justifiable and defensible. Whether they are necessary or even appropriate is a far more difficult question but one that we must inevitably face.

A generous and permissive society accepts and em-

braces these costs as long as they are distributed to all subscribers and are not visibly attached to increased taxes. How long can this compassionate society support the escalating cost of medical care when this cost competes with education, care for the indigent and homeless, and social programs that have become a fixture in our culture? End-stage renal disease benefits, which include both dialysis and transplants, were embraced by our legislative respresentatives some years back. The estimated cost of this isolated, single gesture of generosity will reach $6.3 billion in 1992.[2] Our society's social values have changed over the past 100 years from a personalized approach dependent on individual initiative to a current philosophy that states that health care is a right and that the federal government must see to it that everyone enjoys that right to the fullest degree possible. Future developments are glaringly apparent. Five states now require insurance companies to cover infertility treatment including in vitro fertilization. Last year (1988) the average cost of diagnostic and medical treatments for infertility was more than $2500 per couple and if in vitro fertilization were involved the median cost for each attempt at conception was $5000 to $6000. At the present time only about 10% to 15% of women undergoing the procedure once may expect to have a successful pregnancy. A current effort is being made to introduce into congress legislation that would mandate full infertility coverage in the health insurance packages offered to 3 million government workers. The sponsor of this measure (Representative Pat Schroeder, Democrat of Colorado) has asserted "reproductive organs are a very important part of your bodily function. If they don't appear to be functioning, they ought to be covered by your health insurance." The proposal mandates that health plans cover "family building activities" and these are defined in the legislation as "medical procedures necessary to overcome infertility so as to achieve pregnancy and to carry it to term, and necessary expenses related to the adoption of a child."

To what degree has the blossoming of medical technology contributed to escalation in the costs of the health care system? In any such consideration technology must be interpreted broadly rather than focusing only on isolated examples that can be identified as cost effective. Medical technology is said to have accounted for 15% to 25% of the increased cost of hospital care over the past decade. However, if adjustments are made for systemic general inflation then within the real growth category medical technology accounts for 60% to 70% of the increase![3] New technologies have provided more efficient and accurate means to diagnose or exclude disease, but generally only achieve palliation rather than cure. Health care specialists for the most part concede the influence of technology. The President's Biomedical Research Panel concluded that ". . . new health care technology is a major cause of the large yearly increases in national health expenditures."[5] Not only has the proliferation of expensive instrumentation been an issue but the people required to run the equipment and deliver the services also become more numerous, specialized, and expensive.

The impact of technology on medical education offers another paradox that is unsettling in many respects. The student learns that the services to be given involve a great deal of scientific technology and eventually mastery of the technology becomes the student's preeminent aim in contrast to the traditional personalized involvement. Technology will always eventually win out over the more humanistic approach in medicine. After embracing the skills of technology, the abandonment of traditional "hands on" care frequently follows. In a final examination this year a student was asked how to diagnose a breech presentation and position. The immediate response was ultrasonography. That student was completely unfamiliar with and frankly rather disinterested in the classic maneuvers of Leopold. Inasmuch as the technology has become so overwhelming and the specialization so fragmented for the patient, we must now rely on others to focus on the patient as a total personal entity. These professionals—family practitioners, physician assistants, nurse practitioners—are attempting to repersonalize a health care system that has become so involved in abstract impersonal technology that it has often lost sight of the total patient it is supposed to serve.

I would suggest that the physician today must, for the first time, accept a second role in the pursuit of his specialty. He must act not only as a practitioner concerned with the health and care of his patient but also as a uniquely informed member of a society faced with spiraling health care costs and the need to make informed decisions about the use and role of technology as it develops within the spectrum of health care services. He is part of this larger society that depends on his decisions and his interpretation of the place and critical need for the technologic advances that are developing. He must do this in a prudent and conscientious philosophy that transcends ego support and defensive mechanisms.

Physician concerns over cost containment and a thrust toward a more prudent approach to the advent of technology have yet to seriously emerge. A rather indifferent attitude toward any process of selectivity seems to be the general rule. After listening to a litany of two ultrasonographic examinations and a CT scan that preceded an operation for a dermoid cyst, one of our senior faculty grumbled that the added expense to this patient multiplied so many times over in our com-

munity would go a long way toward solution of the problem of the homeless in Seattle! The physician who will search carefully for a service station that sells gasoline for a few pennies less will casually order a $250 ultrasonographic examination without a second thought.

It has become almost a reflex reaction in many medical communities to request an ultrasonographic study or CT scan to confirm a clearly palpable adnexal mass. There are circumstances in which this may be appropriate but when the findings on examination clearly require and justify surgical exploration the value of the study is questionable. The character of the sonogram may lead the physician to suspect either a benign or malignant neoplasm but clearly surgical exploration is required. The value of the study, then, primarily is to the physician in clarification of his role and support of his decision. The value to the patient remains speculative.

We have enthusiastically applauded the value of electronic fetal monitoring, which is currently used in roughly one half of obstetric cases at an annual cost of $400 million, and some now recommend its use in every delivery.[2] There is little evidence that it has had an effect on fetal outcome assessed by current statistics. A National Institutes of Health consensus conference concluded that there was no evidence that routine ultrasonographic examination in every pregnancy would improve pregnancy outcomes. Yet our fascination and enthusiasm for this procedure has even prompted a highly respected authority in our field to argue for its inclusion in the management of every pregnancy—if only to "help parents bond with their baby." His arguments may seem appropriate but again certainly fail to effectively address the quandry of cost effectiveness.[6]

The tendency to insert new technology into proved conventional approaches to diagnosis seems almost irresistible. In a review of case lists of applicants for American Board examinations some candidates routinely examined every patient with abnormal uterine bleeding with hysteroscopy before curettage, despite the additional cost and the acknowledged reality that the added exercise would seldom prove of benefit.

Intrigued by the obvious question, we carried out a rather interesting study within our department. The medical records of 112 consecutive patients referred over a 4-month interval for treatment of gynecologic malignancy were reviewed. The only study requirement was that the referred patient have some form of prior diagnostic imaging—ultrasonography, CT scan or MRI—and that surgery be performed within 8 weeks of that imaging. A retrospective review of the 40 patients who qualified determined that the radiologic diagnostic accuracy when compared with the surgical findings was only 52% and that in only five of the 40 cases did these adjuvant diagnostic imaging studies contribute information that actually modified or changed the clinical management! In another pilot study from our institution we were interested in the evaluation of the additive value of MRI imaging in cervical malignancy. This study showed that among a small series of patients undergoing radical surgery for cervical cancer, MRI imaging was actually less accurate than clinical examination in estimating the extent of disease defined by the final surgical pathology, yet this practice has already become routine in some centers.

Some form of internal audit must be developed to objectively evaluate and control the use of our expanding technology among our professional community. Third-party payers will not indefinitely provide us with unlimited financial access to expensive technology without a demonstrable savings in return. We will indeed be called to task by cost accounting segments of our society who are unmoved by emotional arguments. The public cries out for an increasing use of technology under the impression that it saves lives and improves medical care. When this can be shown, its selective introduction into the profile of medical care should be welcomed. Perhaps the bottom line of our judgment must rest with the traditional yardstick "has this procedure changed or improved the management in this specific patient." Too frequently it merely serves to reassure the physician, to bypass traditional approaches that will yield the same result, or to document observations that have already clearly defined the approach to treatment.

Technologic advances have enormous potential and their development must be encouraged. Yet our eagerness to precipitously embrace them, ignoring their imperfections and disdaining criteria for suitability, stands out in sharp contrast with the tradition of analytic reasoning so firmly established in other professional decisions we make in the practice of medicine. Because they represent new approaches that capture the imagination we have rushed to introduce it into practice without caution and discrimination.

Medical technology has indeed emerged as a form of tyranny—a complex and often attractive form of tyranny indeed—but nevertheless a symbol of what may be a decisive factor in the determination of whether medical practice as we know it survives. The issue at stake is more than merely cost accounting. It also involves an element of intellectual and ethical honesty. I plead not for a disregard of this technology but only for its selective and judicious inclusion mindful of the significant impact it may well have on the structure of our society and our medical practice. We are part of a larger society that must now face agonizing decisions that involve the expanding subsidy for health care. We have continually sidestepped any responsibility for crit-

ical decisions with regard to the appropriate role for our developing medical technology. Somewhere the first steps must be taken. I would submit that the responsibility may well rest on the guidance of distinguished professional societies such as the one you and I enjoy.

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Prophylactic intrapartum amnioinfusion: A randomized clinical trial

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Amnioinfusion was performed in a prospective, randomized trial of 60 women in the latent phase of labor with oligohydramnios, as defined by an amniotic fluid index ≤5.0 cm. All fetuses were at least 37 weeks' gestational age, had normal baseline fetal heart rate variability, and no clinically significant fetal heart rate decelerations at the outset. Subjects in the amnioinfusion group (n = 30) were titrated to and maintained at an amniotic fluid index level ≥8.0 cm throughout labor. In the group receiving amnioinfusion, significantly lower rates of meconium passage (p = 0.04), severe variable decelerations (p = 0.04), end-stage bradycardia (p = 0.05), and operative delivery for fetal distress (p = 0.002) occurred. Significantly higher umbilical arterial blood pH values were also noted in the infusion group (p = 0.02). We conclude that prophylactic intrapartum amnioinfusion is an important technique for the reduction of intrapartum morbidity. (Am J Obstet Gynecol 1990;162:1370-5.)

Key words: Amnioinfusion, amniotic fluid index, fetal distress

Amniotic fluid has many important functions during pregnancy, including protection of the umbilical cord from compression. In rhesus monkey preparations, it has been shown that removal of amniotic fluid results in variable decelerations in the fetal heart rate (FHR) that resolve when the lost fluid volume is replaced.[1] The inverse relationship between amniotic fluid volume and FHR decelerations has been confirmed in humans by Rutherford et al.[2] Therefore it is reasonable to assume that cord compression, as evidenced by variable decelerations, will be more frequent with decreased amniotic fluid volume. Clinically, oligohydramnios can occur in postdates pregnancies, intrauterine growth retardation, fetal anomalies, or spontaneous rupture of the membranes.

Transvaginal infusion of saline solution into the amniotic cavity (amnioinfusion) can ameliorate variable decelerations of the FHR during labor. Miyazaki and Nevarez[3] found that amnioinfusion led to complete resolution of repetitive variable FHR decelerations in 51% versus 4.2% in control subjects. Nageotte et al.[4] noted significantly fewer variable decelerations in women with preterm premature rupture of fetal membranes who received prophylactic intrapartum amnioinfusion. The group that did not have amnioinfusion was also noted to have a higher cesarean delivery rate for fetal distress. More recently, Wenstrom and Parsons[5] noted a lower rate of meconium aspiration among women who had amnioinfusion and who had thick meconium during labor.

Sarno et al.[6] evaluated the amniotic fluid volume in laboring women using the amniotic fluid index.[7] A significantly increased rate of cesarean delivery for fetal distress and 1-minute Apgar scores less than 7 were associated with an amniotic fluid index value in early labor of ≤5 cm. In addition, decreased FHR variability, severe variable decelerations, and prolonged FHR decelerations were more common with decreased amniotic fluid index.

Despite the efficacy of amnioinfusion in the treatment of variable decelerations, 10 to 25 minutes is usually required before a "therapeutic" volume is instilled by means of gravity flow. This may preclude the technique when rapid intervention is warranted. We hypothesize that a more optimal time for amnioinfusion among those at risk for intrapartum morbidity is before the occurrence of significant FHR abnormalities or the passage of meconium. The purpose of this study was to determine the efficacy of prophylactic intrapartum amnioinfusion in term gestation (≥37 weeks) with amniotic fluid index values ≤5 cm.

Material and methods

During the 6 months from Oct. 1, 1988, through March 31, 1989, laboring women with oligohydram-

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The opinions expressed herein are strictly those of the authors and do not necessarily represent the opinion of the United States Army or the Department of Defense.

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nios (amniotic fluid index ≤5 cm) at Los Angeles County/University of Southern California Women's Hospital were evaluated for participation in the study. Criteria for entry included singleton gestation, vertex presentation, ≤4 cm of cervical dilation, ≥37 weeks' gestation, normal baseline FHR variability, and estimated fetal weight >2500 gm. Patients were excluded for any of the following reasons: late decelerations, moderate or severe variable decelerations, vaginal bleeding, chorioamnionitis, meconium-stained amniotic fluid, fetal anomalies, or uterine anomalies. All subjects participating in the Institutional Review Board–approved study were enrolled with written, informed consent. Consenting women were placed in one of two groups according to a table of random numbers, the randomized permuted block technique ($n = 6$), and opaque, sealed envelopes. The two groups consisted of those with an amniotic fluid index ≤5 cm but receiving no amnioinfusion (controls) and those with an amniotic fluid index ≤5 cm who received prophylactic amnioinfusion.

Amnioinfusion was accomplished in the manner outlined by Miyazaki and Nevarez[3]; 250 ml of normal saline solution warmed to 37° C, was infused through an intrauterine pressure catheter at a rate of 10 to 20 ml/min. Infusions of 250 ml were repeated until an amniotic fluid index of at least 8 cm was reached. External uterine tokodynamometry was used during the actual infusion process. Patients receiving infusions underwent hourly amniotic fluid index determinations, and repeat amnioinfusion was performed whenever the amniotic fluid index fell below 8 cm.

With a value of $p = 0.05$ used to establish statistical significance and assuming a β-error of 0.2, a calculation of power for the study suggested that a minimum of 30 subjects be assigned to each study group. The power calculation was based on the differential cesarean delivery rates for fetal distress in the infusion versus control groups of Miyazaki and Nevarez[3] (14.8% versus 47.6%, respectively).

The FHR tracings in the last 40 minutes before delivery were evaluated in terms of baseline heart rate, reactivity, beat-to-beat variability, and the presence of variable or late decelerations. Variable decelerations were graded as mild, moderate, or severe according to the criteria of Kubli et al.[8] Fetal heart rate reactivity was considered present if a single acceleration of the FHR of 15 beats/min from baseline persisting for 15 seconds or more was noted. Intrapartum decelerations were considered significant only if noted with 50% or more of contractions. All heart rate strips were evaluated by the same examiner (A. S.), who was unaware if the patient received amnioinfusion. Statistical comparisons were performed with Student's t test, χ^2, or Fisher's exact test.

Results

Informed consent was obtained for 60 patients who met the inclusion criteria for the study. No eligible study candidate refused to participate. Thirty subjects were randomized into each group. The treatment and control groups were similar for maternal age, parity, gestational age, and amniotic fluid index (Table I). In addition, the groups had statistically similar proportions of nulliparous women, postdates pregnancies (estimated gestational age ≥ 41 weeks), and patients with intact membranes at the time of admission to labor and delivery. However, the interval from membrane rupture to delivery was significantly longer ($p = 0.01$) in the infusion group.

The infusion group required an average of 1.6 ± 0.3 infusion sequences to attain an amniotic fluid index value ≥8.0 cm. The total infusion volumes of normal saline solution required ranged from 250 to 1000 ml (mean, 379 ± 141 ml; Table II). There was no significant difference between nulliparous and multiparous women in terms of infusion volumes required. Four of 30 women (13%) required reinfusion during labor, probably as a result of fluid loss as evidenced by a decrease in the amniotic fluid index below 8.0 cm. Two women (7%) initially failed to attain amniotic fluid index values of 8 cm after amnioinfusion. There was notable vaginal leakage during the infusion process. After engagement of the fetal head, one of these subjects later received successful infusion.

One woman in the infusion group experienced an umbilical cord prolapse during a midpelvic forceps rotation attempt for a persistent occiput transverse position. An unremitting bradycardia ensued and a depressed infant was delivered by cesarean section. Until the forceps trial, the intrapartum fetal tracing had average baseline fetal heart rate variability and sporadic mild variable decelerations.

Intrapartum the amnioinfusion group had significantly less frequent meconium passage ($p = 0.04$), end-stage bradycardia ($p = 0.01$), and operative deliveries for fetal distress ($p = 0.002$) (Tables III to V). When corrected for the single patient in which the amnioinfusion failed, the infusion group had significantly fewer severe variable decelerations than control subjects ($p = 0.04$). At delivery the mean umbilical arterial blood pH value in the infusion group (7.29 ± 0.03) was significantly higher than that of the control group (7.23 ± 0.09) ($p = 0.02$). No neonate sampled in the infusion group ($n = 17$) had an umbilical arterial blood pH <7.20, whereas 28% of the arterial pH values sampled in the control group ($n = 18$) were less than 7.20 ($p = 0.015$, Fisher's exact test).

Comment

Variable decelerations of the fetal heart rate are probably caused by umbilical cord compression.[9, 10] Such

Table I. Patient characteristics

	Infusion group (N = 30)	*Control group (N = 30)*	*p Value*
Age (yr)	23.9 ± 5.6	24 ± 5.8	NS
Parity (mean)	0.6 ± 1.5	0.8 ± 1.3	NS
Nulliparous women	15 (50%)	19 (63%)	NS
Multiparous women	15 (50%)	11 (37%)	NS
Estimated gestational age (wk)	40.2 ± 1.4	40.7 ± 1.9	NS
Postdates pregnancies	14 (47%)	17 (57)	NS
Amniotic fluid index (cm)	3.2 ± 1.4	2.7 ± 1.6	NS
Rupture of membranes-to-delivery interval (hr)	16.8 ± 12.1	10.1 ± 6.5	0.01*
Intact membranes at admission	15 (50%)	22 (73%)	NS

*Student's *t* test.

Table II. Amnioinfusion

Mean volume infused (ml)	
Nulliparous women	375 ± 148
Multiparous women	388 ± 124
Overall	379 ± 141
Reinfusions	
Nulliparous women	2 (7%)
Multiparous women	2 (7%)
Total	4 (14%)
Failed infusions*	
Nulliparous women	1 (3.5%)
Multiparous women	1 (3.5%)
Total	2 (7.0%)

*Failed amniotic fluid volume expansion caused by leakage of amnioinfusate.

compression quite logically will be more frequent when the amniotic fluid volume is diminished. The probable benefit of amnioinfusion relates to restoration of the intrauterine fluid volume, which minimizes umbilical cord compression.

Maintenance of an adequate amniotic fluid volume provides protective cushioning of the umbilical cord during labor. On the basis of our preliminary experience, amnioinfusate that is not retained in utero provides little benefit other than the effect of lavage. Hourly intrapartum amniotic fluid index assessment is a labor-intensive process that our preliminary experience suggests may be unnecessary. Study subjects who had leakage of significant volumes of fluid usually did so during the initial infusion. After an adequate amniotic fluid index was attained in our subjects, the tendency (in 87% of women who had infusion) was for the fluid to remain in the intraamniotic space. Presumably, the fetal head well applied to the cervix serves to impede egress of fluid from the uterus.

Patients with oligohydramnios (amniotic fluid index ≤ 5.0 cm) as a result of ruptured fetal membranes probably represent a group clinically different from the patients with oligohydramnios with intact fetal membranes. Placental insufficiency, as manifested by intrauterine growth retardation or the presence of late FHR decelerations, might have theoretically played a role in the development of FHR changes among our subjects. To control for this possibility, we excluded fetuses with ultrasonographic weight estimates <2500 gm (i.e., fetuses with intrauterine growth retardation). None of the "fetal distress" diagnosed in either group was on the basis of late decelerations. Moreover, the infusion and control groups had statistically similar proportions of patients with intact membranes at admission, and the mean neonatal birth weights in both groups were similar. Therefore we conclude that both the infusion and control groups were similar with regard to the pathophysiology of oligohydramnios and subsequent FHR changes.

An amniotic fluid index ≥8.0 cm was chosen as a postinfusion goal because it was above the 5.0 cm "at risk" level and was well beyond the quoted range of measurement error (±1 cm).[11] However, an amniotic fluid index value of 8.0 cm is still significantly less (1 SD) than the mean amniotic fluid index for third-trimester gestations.[6] The mean volume infused in our study (379 ml) differed from that of Nageotte et al.[4] (1160 ml). Perhaps amnioinfusion of larger volumes would have resulted in more significant differences in the outcomes between our study and control groups. We hope further to clarify this issue with an ongoing clinical trial of prophylactic amnioinfusion at our institution.

The overall rate of nuchal cords in our study population, 25% (15/60), is in agreement with quoted rates.[12] Nuchal cords did not occur significantly more frequently in either group. However, twice as many nuchal cords occurred in the infusion group, lending further credence to the protective effect of adequate amniotic fluid volume during labor. Miyazaki and Taylor[13] noted complete resolution of variable decelerations in 10 of 11 women with nuchal cords. Thus maintenance of an adequate amniotic fluid volume through amnioinfusion may prove to be of benefit in preventing or reducing the occurrence of worrisome variable or prolonged FHR decelerations that often lead to intervention with this common problem.

Umbilical cord prolapse can occur during midpelvic forceps procedures. Therefore we believe that the cord prolapse in this study occurred as a result of the at-

Table III. Intrapartum characteristics

	Infusion group (N = 30)	*Control group (N = 30)*	*p Value*
Maternal temperature >100.4° F (38° C)	6 (20%)	2 (7%)	NS (0.06)
Meconium	4 (13%)	11 (37%)	0.04*
Fetal tachycardia	2 (7%)	4 (13%)	NS
Nonreactivity	5 (17%)	3 (15%)	NS
Decreased variability	4 (13%)	5 (17%)	NS
Late decelerations	0	0	NS
Variable decelerations			
Mild	7 (23%)	8 (27%)	NS
Moderate	7 (23%)	5 (16%)	NS
Severe	2 (7%)†	8 (27%)	0.04*
Total	16 (53%)†	21 (70%)	NS
End-stage bradycardia	1	7	0.05

*Fisher's exact test.

†Corrected for failed amniotic fluid volume expansion caused by leakage of amnioinfusate.

tempted midpelvic forceps rotation rather than amnioinfusion. Miyazaki and Nevarez[3] also noted a single case of cord prolapse and estimate a prolapse rate of 1 per 400 (0.25%) amnioinfusion patients.[14] This rate compares favorably with the quoted rate of one in 200 (0.5%) among noninfused pregnancies in vertex presentation.[14]

Forceps procedures are done with relative frequency at our institution. For example, seven forceps deliveries were performed for fetal distress in the control group of this study, four of which were midpelvic rotations. Had midpelvic operative procedures not been performed, we suspect that the number of emergency cesarean deliveries for fetal distress in the control group would have increased to at least eight (27%) versus one (3%) in the infusion group ($p = 0.025$, Fisher's exact test).

With regard to operative delivery for fetal distress, we noted that two women from the control group who ultimately were delivered vaginally were taken to the operating room for possible cesarean delivery for prolonged FHR decelerations during the first stage of labor. In both cases, the FHRs were noted to have recovered in the operating room. Therefore both women were allowed to continue in labor. One patient received a single intravenous dose of terbutaline (0.25 mg) during the fetal bradycardia, whereas the other recovered spontaneously. The second woman was taken a second time to the operating room for fetal bradycardia that also relented. We suspect that in many facilities both women might have undergone cesarean delivery.

Intrapartum febrile morbidity (temperature ≥ 100.4° F or 38.0° C) did not occur significantly more frequently in the infused group, although a trend is present (Table III). It is not likely that the intrapartum temperature elevations were directly caused by the amnioinfusion procedure itself. Rather, we suspect that the increased rate of intrapartum febrile morbidity was related to the significantly longer labors. In addition, women in the infusion group were subject to significantly longer periods with ruptured membranes, more pelvic examinations, and longer periods of internal monitoring. Curiously, even when comparing only women who were delivered vaginally, the infu-

Table IV. Operative intervention

	Infusion group (N = 30)	*Control group (N = 30)*	*p Value*
Intervention for fetal distress			
Cesarean	1* (3%)	4 (13%)	NS
Forceps	0	7 (24%)	0.01†
Vacuum	0	0	NS
Total	1* (3%)	11 (37%)	0.002†
Intervention for reasons other than distress			
Cesarean	3 (10%)‡	2 (7%)	NS
Forceps	5 (17%)§	1 (3%)	NS
Vacuum	0	0	NS
Total	8 (27%)	3 (10%)	NS

*Corrected for cord prolapse as a result of use of forceps for occipitotransverse position.

†Fisher's exact test.

‡All for failure to progress in labor–cephalopelvic disproportion.

§Three elective forceps deliveries and two for occipitotransverse positions.

Table V. Neonatal outcome

	Infusion group (N = 30)	*Control group (N = 30)*	*p Value*
Birth weight (gm)	3327 ± 437	3305 ± 477	NS
Nuchal cords	11 (37%)	5 (7%)	NS
Apgar scores			
1 min	8.1 ± 1.4	7.8 ± 1.4	NS
5 min	8.9 ± 0.6	8.9 ± 0.2	NS
Apgar scores <7			
1 min	0*	3 (10%)	NS (NS*)
5 min	0*	0	NS (NS*)
Neonatal sepsis	1 (3.5%)	0	NS

*Corrected for cord prolapse as a result of forceps use for occipitotransverse position.

sion group still had significantly longer rupture of membranes-to-delivery intervals ($p < 0.01$). Neither Nageotte et al.[4] nor Wenstrom and Parsons[5] have noted significant differences in terms of length of labor or febrile morbidity. Currently we cannot explain why those in our infusion group had longer labors.

In summary, this study has shown that laboring women at or beyond term with oligohydramnios apparently benefit from prophylactic amnioinfusion. The procedure of amnioinfusion is simple, safe, low-cost, and significantly reduces the incidence of intrapartum morbidity. Further expanded evaluations should be undertaken to clarify the indications, application, and efficacy of this technique. Limited careful use of amnioinfusion does not seem unreasonable based on our current understanding, but caution should be used before widespread application of this intervention is contemplated.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. ROBERT GOODLIN, Denver, Colorado. Dr. Strong, Althabe et al.[1] described the same sort of response in the 1950s and 1960s. They related the incidence of fetal distress and the length of labor to amniotic fluid volume as you have done. However, they stated that the vagal heart rate changes were a result of head compression, which makes more sense to me than cord compression. In your ultrasonographic examinations, have you any evidence that cord compression is really relieved with amnioinfusion?

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DR. JULIAN PARER, San Francisco, California. I would like to expand on Dr. Goodlin's question and ask for your comments. We need to separate variable decelerations into active-stage (before second-stage) variables and second-stage variables. There is now much evidence that head compression is responsible for variable decelerations in the second stage of labor. One example is the almost universal occurrence of severe variables on traction with forceps. I firmly believe that the majority of severe variable decelerations and end-stage bradycardias seen in the second stage are caused by dural stimulation from head compression with subsequent vagal activity. You have evidence to the contrary in that you did relieve the end-stage bradycardia with amnioinfusion. I understand that Nageotte et al.[1] could not abolish second-stage variables with amnioinfusion.[1] Your results are at variance with theirs.

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DR. STRONG (Closing). Dr. Goodlin, we have inferred relief of cord compression because we have been able to demonstrate by the amniotic fluid index an increase in the amniotic fluid volume. Miyazaki and Nevarez,[1] in their original article, suggested that the majority of the fluid reaccumulated in the lower uterine segment. You could interpret this to indicate cushioning to the fetal head. In our article we really did not address the question of where the fluid acccumulated. However, it is my feeling that it is the cord rather than the head that is protected by expansion of amniotic fluid volume.

Dr. Parer, the difference between my article and the

one by Nageotte et al. (and other articles reporting amnioinfusion) is that we determined the amniotic fluid volume on a regular, hourly basis. That determination is important to ensure that throughout labor amniotic fluid volume is retained in utero to provide cushioning, or whatever it is, during the course of labor. As the mother begins pushing, much of the amniotic fluid may be expelled. I reiterate that you not only expand the fluid volume, but that you need to maintain it during labor.

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Ultrasonography-guided early amniocentesis in singleton pregnancies

Frederick W. Hanson, MD, Regina L. Happ, MD, Frances R. Tennant, PhD, Stacy Hune, MS, and Ann G. Peterson, RN, MN
Davis, California

Between October 1, 1986, and September 30, 1987, 1721 amniocenteses were performed at the University of California, Davis, Medical Center. Of these procedures 527 (30.6%) were early amniocenteses. Medical records were reviewed for maternal age, amniocentesis indication, color of amniotic fluid, gestational age, frequency of needle insertion, complications of amniocentesis and delivery, results of prenatal testing, and pregnancy outcome. Complete follow-up data were available for 517 (98.1%). There were 10 miscarriages before 28 weeks' gestation (1.9%), one loss after 28 weeks (0.2%), and one stillbirth (0.2%), resulting in a total postprocedural loss rate of 2.3%. Miscarriage within 2 weeks of amniocentesis occurred in four subjects (0.8%). (AM J OBSTET GYNECOL 1990;162:1376-83.)

Key words: Early amniocentesis, discolored amniotic fluid, miscarriage, stillbirth, amniotic fluid leakage

Prenatal diagnosis of chromosomal biochemical and neural tube defects has been widely accepted as a routine procedure in the management of obstetric patients. Amniocentesis has customarily been performed between 16 to 18 weeks' gestation. Patients and physicians, however, have increasingly requested earlier diagnosis for reassurance of the normality of the pregnancy or to allow earlier and safer interruption of pregnancy if indicated by detection of a fetal abnormality.

A spectrum of diagnostic procedures is now available to meet these demands and includes chorionic villus sampling (transcervical or transabdominal), earlier amniocentesis, and conventional amniocentesis.

In 1987 we published our initial report on earlier amniocentesis.[1] That report covered an extended time period with increasing operator experience and frequent modification of technique. Continuous ultrasonographic monitoring during amniocentesis was not used for the time period covered by that publication. It is the purpose of this report to reevaluate our experience performing earlier amniocentesis with the use of continuous ultrasonographic guidance.

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6/6/20284

Methods

The prenatal diagnosis program at the University of California, Davis, has been previously described.[2] More than 12,000 amniocentesis procedures have been performed since inception of the program in 1976. During the period covered by this study (October 1, 1986, through September 30, 1987) 1721 amniocentesis procedures were performed. The majority were performed by one of the authors (F. W. H.). Of these procedures 527 were accomplished before week 15 since the last menstrual period, and they are the subject of this report.

The data were evaluated for amniocentesis indication; gestational age at the time of amniocentesis (weeks since last menstrual period ± 1 week); color of amniotic fluid; pregnancy complications before amniocentesis, delivery complications, amniocentesis complications, and pregnancy outcome. For comparison with previously published studies pregnancy loss data were divided into the following categories: 2 weeks after amniocentesis, <28 weeks' gestation (miscarriage), ≥28 weeks' gestation (stillbirth), and neonatal death (within 1 week of birth). Loss data were further evaluated as to possible or probable relationships to amniocentesis.

The technique of amniocentesis used in our program was previously reported.[2] This has been modified to include continuous ultrasonographic monitoring to guide placement of the needle and monitor fetal movement during amniocentesis (Fig. 1). We use either an RT 3000 machine (General Electric, Milwaukee) or an ATL Ultramark 4 machine (Advanced Technology Laboratories, Inc., Bothell, Wash.) for this purpose.

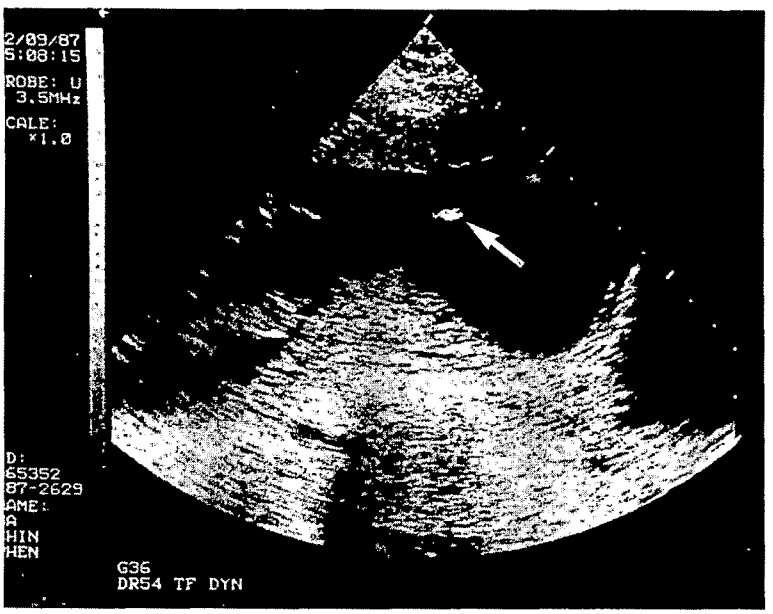


Fig. 1. Example of continuous ultrasonographic monitoring of needle placement in early amniocentesis. *Arrow* indicates tip of needle within amniotic fluid.

During the period covered by this study a 20 gauge spinal needle was used and a mean of 26 ml of amniotic fluid was removed. Currently we exclusively use a 22 gauge needle and remove approximately 1 ml of amniotic fluid for each week of gestational age.

Amniotic fluid was cultured with the in situ technique of Peakman.* Fifteen clones and five karyotypes were examined and analyzed. The experience of our cytogenetic laboratory in culture of amniotic fluid from 10- to 14-week pregnancies has recently been reported.[3] The mean time in culture is 8.8 days (SD, 1.5 days).

The program Microsoft Works and Statview 512+ (Abacus Concepts, Inc., Berkeley, Calif.) was used on a MacIntosh Plus microcomputer (Apple Computers, Cupertino, Calif.) to prepare summary tables.

Table I. Indications for amniocentesis

	No. of patients	%
Maternal age	462	87.7
Maternal anxiety	33	6.3
Family history/prior child with chromosome abnormality	20	3.8
Prior child with multiple congenital abnormalities	5	0.9
Family history/prior child with neural tube defect	5	0.9
Pregnancy at risk for metabolic disease	1	0.2
Fetal abnormality on ultrasonography	1	0.2

Results

The demographic data of the study population were not different from those published in our previous studies.[1, 2] The indications for amniocentesis are seen in Table I.

A total of 1721 amniocenteses were performed during the study period. There were 527 amniocenteses, representing 30.6% (527/1721) of the total, performed before 15 weeks since the last menstrual period. the patient distribution by gestational age is seen in Table II.

The frequency of needle insertion is shown in Table III. A total of 92% of the amniocenteses were successfully performed with a single needle insertion. One patient required retap because of failure of culture growth as a result of inadequate fluid volume obtained at amniocentesis.

The volume of amniotic fluid obtained at amniocentesis varied from 5 to 36 ml with a mean of 26.3 ml in those patients with a normal outcome. The mean fluid volume removed from those patients who had a fetal loss was 22.8 ml, varying between 12 to 36 ml.

Discolored amniotic fluid was obtained from 5.1% (27/527) of the amniocenteses. Only 8.3% (1/12) of the patients who had fetal loss had discolored fluid.

A total of 1.5% (8/527) patients required rescheduling. Seven were determined to be too early and one was because of culture failure.

*David Peakman and Associates Reproductive Genetics Center, P.C., Denver, Colo.

Table II. Gestational age at the time of amniocentesis on the basis of measurements of biparietal diameter

Biparietal diameter (cm)	*Gestational age (wk)**	*No. of patients*	*%*
<1.6	10	2	0.4
1.6-1.9	11	9	1.7
2.0-2.2	12	46	8.7
2.3-2.6	13	215	40.8
2.7-2.9	14	255	48.4
TOTAL	—	527	100

*Weeks since last menstrual period ± 1 week.

Table III. Frequency of needle insertion

No. of insertions	*Frequency*	*%*
1	486	92.2
2	37	7.0
3	4	0.8
TOTAL	527	100

Table IV shows the number of patients who had complications within 2 weeks of amniocentesis. A total of 503 (95.4%) did not have problems. Four patients (0.8%) had an unanticipated pregnancy loss within 2 weeks of amniocentesis. No data concerning potential complications were available for seven patients (1.3%).

Eight patients (1.5% of the total) had amniotic fluid leakage of several days' duration after amniocentesis. One of these patients, who had been bleeding and cramping before amniocentesis, miscarried a chromosomally normal fetus 3 weeks after amniocentesis. The pregnancy outcomes for the eight patients with amniotic fluid leakage are seen in Table V.

Table VI lists delivery complications. Vaginal delivery without complication was undergone by 72.4% of subjects (366/505). Cesarean section was the route of delivery for 22.8% (115/505). Fourteen patients (2.8%) had a number of complications such as premature labor, premature rupture of membranes, postpartum hemorrhage, retained placenta, and pregnancy-induced hypertension that were not considered of sufficient frequency to list separately.

Pregnancy outcome for all patients who underwent early amniocentesis is listed in Table VII. A total of 92.4% (474/513) of patients were delivered of a normal child.

Twelve patients (2.3%) were seen with a variety of outcomes such as macrosomia, hydrocephalus, cystic fibrosis, diaphragmatic hernia, congenital glaucoma, absent hand, hyperbilirubinemia, and dislocated knee and were placed in a category of outcome called "other." These were of insufficient frequency to rate

Table IV. Complications of early amniocentesis within 2 weeks of the procedure

	No. of patients	*%*
None	503	95.4
Fluid leakage*	8	1.5
Data not available	7	1.3
Miscarriage <2 wk	4	0.8
Cramping	3	0.6
Bleeding	3	0.6

*One patient included in both fluid leakage and miscarriage.

Table V. Pregnancy outcome in those patients with amniotic fluid leakage after amniocentesis

Patient	*Delivery*	*Pregnancy outcome*
101	Vaginal delivery	Leaked ×2 days; normal term
161	Curettage	Fetal death 3 weeks after amniocentesis
434	Vaginal delivery	Normal term
454	Vaginal delivery	Obstetric complication, incompetent cervix; normal term
657	Vaginal delivery	Normal term
810	Cesarean section repeat	Leaked for 12 hr, cesarean section repeat; normal term
975	Vaginal delivery	Normal term
1497	Vaginal delivery	Born with dislocated knee at term

placement in individual categories. Four patients, representing 0.8% of the total (4/527), were seen with fetal death before amniocentesis.

Six patients (1.1%) had either structural or chromosomal abnormalities detected and chose to terminate their pregnancies. Ten patients (1.9%) were lost to follow-up.

Twelve patients, representing 2.3% of the total (12/523), had pregnancy losses at some point after the amniocentesis. Table VIII lists four cases or 0.8% (4/523) that appear to be amniocentesis-related although patient No. 161 was bleeding and cramping before amniocentesis. Table IX describes those losses that probably are not related to amniocentesis; eight cases are listed, representing 1.5% (8/523) of the total. If cases that are clearly not related to amniocentesis are eliminated such as Nos. 791 and 1146, the overall loss rate is 1.9% (10/523). The remaining six cases all had significant abnormal ultrasonographic findings or preamniocentesis pregnancy complications that could have been significant enough to explain the cause of the pregnancy loss. These factors included preamniocentesis bleeding with and without cramping, subamniotic hematoma, retroplacental fibroid or mass, and tight nuchal cord.

The overall loss rate of desired pregnancies in this study was 4.4% (23/517). This represents a combina-

tion of losses before amniocentesis (4), losses after amniocentesis (11), stillbirth (1), elective termination of a normal pregnancy (1), and elective termination of abnormal pregnancies (6). This figure includes only pregnancies with known outcomes.

Comment

Concerns with regard to the safety and hazards of prenatal diagnostic procedures have resulted in numerous reports with regard to midtrimester amniocentesis.[2, 4-8] Reported fetal loss rates have ranged from a low of 0.3%[8] to 2.89%.[4] A recently published report that evaluates the safety and efficacy of chorionic villus sampling showed a combined loss rate (spontaneous and missed abortion, termination of abnormal pregnancies, stillbirths, and neonatal deaths) for desired pregnancy of 7.2% in the chorionic villus sampling group and 5.7% in the amniocentesis group. After data adjustment it was concluded that the difference in loss rate for the two groups was 0.8%.[9]

It is difficult to establish an entirely comparable figure for our study population. Our overall loss rate of desired pregnancies was 4.4%.

In evaluation of procedural risk it is important to realize and consider that performance of these prenatal diagnostic procedures is superimposed on a certain background spontaneous abortion rate. The earlier a procedure is performed, the higher is this rate and the longer is the opportunity for the patient to have a spontaneous abortion. In our previous publications we did not consider background loss data in reporting our results.[1, 2]

It has long been considered that 15% to 20% of recognized pregnancies result in spontaneous abortion before 20 weeks' gestation. Liu et al.[10] followed up 1068 pregnancies that were confirmed to be normal by ultrasonography (before 14 weeks' gestation) until 28 weeks' gestation. They reported an overall 2.7% spontaneous abortion rate with 1.5% occurring before week 16 and 1.2% between 16 to 28 weeks' gestation. They also suggested a slightly higher spontaneous abortion rate (1.8% versus 1.3%) between 11 to 16 weeks' gestation for primigravid patients, as compared with multigravid patients. Threatened miscarriage was associated with a 38% fetal loss rate. This may have been a factor in 42% (5/12) of our losses.

Gilmore and McNay[11] followed up 2144 pregnancies that were established as normal by ultrasonography before 10 weeks' gestation. An overall 2.1% spontaneous abortion rate occurred. This rate tended to increase with increasing maternal age, being 2.6% between ages 35 to 39 years and 13.6% at age ≥40 years. Wilson et al.[11] published a similar study and showed comparable results with an overall spontaneous abortion rate of 2.13% (up to 20 weeks' gestation) and an increasing risk with advancing maternal age. Furthermore it should be noted that the 1976 National Institute of Child Health and Human Development study of amniocentesis published a 3.2% spontaneous abortion rate* for their control group of race, gravidity, and family income–matched women.[4] However, these pregnancies were not shown to be normal by ultrasonography before amniocentesis.

Compared with our previously published total postprocedural loss rate of 4.7%,[1] the figure of 2.3% for this study suggests significant improvement. The addition of continuous ultrasonographic guidance has contributed significantly to this improvement. Increased experience has also contributed. Technically,

Table VI. Delivery complications in patients undergoing early amniocentesis*

Complications	*No. of patients*	*%*
None—vaginal delivery	366	72.4
Total cesarean section	115	22.8
For cephalopelvic disproportion	50	9.9
Repeat	21	4.2
For failure to progress	21	4.2
For breech	12	2.4
For placenta previa	4	0.8
For active herpes	4	0.8
For abruptio placentae	1	0.2
For fetal distress	1	0.2
For oligohydramnios	1	0.2
Other—vaginal delivery	14	2.8
Not available	10	2.0

*Does not include the following patients: 11 pregnancies lost prematurely; 7 pregnancies electively terminated; 4 pregnancies lost before amniocentesis.

Table VII. Pregnancy outcome for 523 patients undergoing early amniocentesis*

Outcome	*No. of patients*	*%*
Normal female	261	50.9
Normal male	213	41.5
Other	12	2.3
Fetus abnormal—terminated	6	1.2
Miscarried <28 weeks' gestation	6	1.2
Prematurity <35 weeks' gestation	6	1.2
Miscarried within 2 wk after amniocentesis	4	0.8
Stillborn	1	0.2
Abnormal child not detected prenatally	1	0.2
Miscarried >28 weeks' gestation	1	0.2
Small for gestational age	1	0.2
Fetus normal—terminated	1	0.2

*Does not include four patients who were first seen with fetal death before amniocentesis and 10 patients with no follow-up.

*A total of 75% (24/32) of the losses occurred before week 29.

Table VIII. Losses probably related to early amniocentesis

ID	*Indication for amniocentesis*	*Pregnancy complications*	*Gestational age at amniocentesis (wk)*	*Ultrasonographic findings*	*Transplacental*	*Fluid volume (ml)*
151	Maternal age	Exposure, viral infection	14.2	Normal singleton	−	26, clear
161	Maternal age	Bleeding and cramping	13.3	Normal singleton	+	16, clear
224	Maternal age	None	13.1	Normal singleton	−	24, clear
890	Maternal age	None	13.9	Normal singleton	+	24, clear

Table IX. Losses possibly/probably not related to early amniocentesis

ID	*Indication for amniocentesis*	*Pregnancy complications*	*Gestational age at amniocentesis (wk)*	*Ultrasonographic findings*	*Transplacental*	*Fluid volume (ml)*
398	Maternal age	Bleeding	14.7	Subamniotic hematoma	−	24, discolored
459	Maternal age	None	13.1	Fibroid or retroplacental mass	−	17, clear
520	Maternal age	Bleeding and cramping	14.2	Normal singleton	+	36, clear
731	Maternal age	Bleeding at 6-10 wk	14.2	Normal singleton	−	24, clear
791	Maternal age	None	14.5	Normal singleton	+	24, clear
1146	Maternal age	None	13.6	Holoprosencephaly	−	24, clear
1385	Maternal age	None	12.0	Normal singleton	−	12, clear
1448	Maternal age	Bleeding, placenta previa	12.8	Normal singleton	−	24, clear

early amniocentesis becomes easy to perform once one gains experience and with that experience confidence. We have learned that certain clinical situations such as patients with extreme obesity, a retroverted uterus with intervening bladder and bowel, or amnion chorion separation with an undulating amnion are best rescheduled although early amniocentesis is technically feasible. Since completion of this study protocol we have further modified our procedure to include exclusive use of a 22 gauge needle and removal of 1 ml of fluid for each gestational week. We have confidence in our laboratory to culture early amniotic fluid.[3] α-Fetoprotein levels can also be assayed and confidently interpreted on these fluids.[12]

In summary, continuous ultrasonographic guidance appears to decrease the risks of early amniocentesis and add to the technical ease of obtaining the amniotic fluid specimens. When combined with in situ cell culture and reliable α-fetoprotein assay it offers patients a viable option for early prenatal diagnosis.

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No. of taps	*Amniocentesis complications*	*Weeks after amniocentesis loss documented*	*Pregnancy course*
1	None	1 wk	Fetal heart tones absent 1 week after amniocentesis
1	Fluid/leakage	3 wk	Fetal death 3 wk after amniocentesis
1	None	3 days	Pregnancy lost 3 days after amniocentesis
1	None	1 wk	No fetal heart tones 1 wk after amniocentesis

No. of taps	*Amniocentesis complications*	*Weeks after amniocentesis loss documented*	*Pregnancy course*
1	None	1 wk	Subamniotic hematoma; bleeding 1 wk before amniocentesis
1	None	4 wk	Fibroid or retroplacental mass; amniocentesis 4/13/87; fetal heart tones present 4/16/87
2	None	3 wk	Pregnancy lost 3 wk after amniocentesis
1	None	4 wk	Bleeding wk 6-10, premature rupture of membranes; fetal death 18 wk; tight nuchal cord ×2
1	None	>16 wk	Amniocentesis 6/24/87; fetal death 10/2/87
2	None	Term	Stillborn; holoprosencephaly on ultrasonography
1	None	4 wk	Fetal death 4 wk after amniocentesis; no complications
1	None	4 wk	Placenta previa and extensive bleeding

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Lewis Shenker, Tucson, Arizona. Hanson et al.[1] presented their first article on this topic at the 1986 meeting of this society. They described 542 procedures performed before 15 weeks' gestation. Only four (0.7%) were done at 11 weeks' gestation; 36 (6.7%) at 12 weeks; and 149 (27.5%) at 13 weeks. The majority

of the described procedures (352 or 65.1%) were done at 14 weeks' gestation. In his discussion, Dr. Goodlin did not think that it was unusual to perform amniocentesis as early as 14 weeks. This observation has even more validity today.

The present article describes the addition of ultrasonographic guidance to the performance of early amniocentesis. Dr. Hanson now does early amniocentesis in 30.6% of his patients, compared with the previous study when early amniocentesis comprised 11.4%. A total of 57 of the 527 procedures were performed in the group at 10 to 12 weeks' gestation. The conventional definition of early amniocentesis is applied to procedures at ≤14 weeks' gestation and possibly justifies the inclusion of 13- and 14-week gestations in both of Dr. Hanson's series. I am very critical of this definition of early amniocentesis and would like to see it modified to include only those procedures performed from 9 through 12 weeks' gestation. Until there is more reported experience at these gestational ages, a true comparison of this procedure with chorionic villus sampling with respect to results and complications will be impossible.

There is decreased pregnancy loss in the recent series compared with the original. Dr. Hanson chooses to credit this to the use of ultrasonographic guidance and increased experience. My prejudice is to give more weight to the latter. Especially with very early amniocentesis, the choice of needle sites is limited; either a favorable site exists or it does not. If a direct perpendicular track to the amniotic sac is not present, my preference is to reschedule the procedure. Measurement of depth from the skin surface will make aspiration of amniotic fluid relatively easy. I have not felt the need for ultrasonographic monitoring during the procedure, but will spend extra time scanning and planning the approach before the needle insertion.

I would like to ask Dr. Hanson two questions. Does he feel confident about the normal range of values for amniotic fluid α-fetoprotein and acetylcholinesterase values at gestational ages of 10 through 14 weeks? How does he manage twins diagnosed by ultrasonography at the time of scheduled genetic amniocentesis at 10 weeks' gestation?

I congratulate Dr. Hanson on his article with regard to this interesting series of early amniocenteses. It will help us to counsel patients in their choice of early versus conventional amniocentesis. I look forward to seeing reports on future series of patients in the early group of 10 to 12 weeks' gestation.

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DR. ROBERT GOODLIN, Denver, Colorado. I remember that you were always a very strong advocate of size 18 needles and am curious why you are suddenly going to size 22. I was intrigued by your interesting sex ratio—many more females than males. Who does your ultrasonic guidance? I know that when I do amniocentesis, if the technician is highly skilled, there is no problem. However, if he or she is less skilled, I obtain fluid less often. My final question is what do you do when your technician finds bradycardia?

DR. RICHARD ALLEN, Portland, Oregon. I discussed this topic with two people who do most of these procedures in Portland. Both prefer chorionic villus sampling in early pregnancy because they believe that when they try amniocentesis earlier than the conventional time they get a higher failure rate. They both stated independently that if they were doing a DNA profile they could get enough fluid, but if they were doing a full chromosome panel they might not be able to get enough fluid for cell cultures to grow. I am curious as to whether you have had any problem with cell cultures growing in these earlier amniocenteses.

DR. HANSON (Closing). I certainly agree with Dr. Shenker's suggested modification of the definition of early amniocentesis. We are now doing 50% of our amniocentesis at <15 weeks' gestation, and 50% of those are at 12 weeks' gestation. Our experience is unchanged. We recently published an article[1] that was a follow-up to our original article[2] on early amniotic fluid α-fetoprotein levels. We are very confident of the values. The SD was very tight. The reliability of acetylcholinesterase is a little different. Dr. Crandall believes that at least down to 12 weeks' gestation it is very, very reliable; below 12 weeks, with experience it is still interpretable. She will present a paper[3] in the fall on this subject. Although I have done a fair number of twins early, I reschedule because I am going to be tapping two sacs and taking a larger total volume of fluid. I have no scientific reason for doing this.

Dr. Goodlin, I have not used an 18 gauge needle in years. There have been articles that suggested 18 gauge needles are associated with increased fetal morbidity so I switched to 20 gauge and now I use 22 gauge exclusively for early amniocentesis. If the needle is to be inserted near the umbilicus or higher I will use a 20 gauge. I can withdraw fluid faster with a 20 gauge than I can with a 22 gauge, and I like to get in and out quickly. I cannot explain the difference in the fetal sex ratio. The ultrasonographers that I work with are superb and I rely on them to help me identify the needle tip because I have my hands full manipulating the needle and watching the ultrasonographic screen. I listen to them to make the needed adjustments. I do find that continuous monitoring is valuable because I can redirect the needle away from the fetus, making midcourse adjustments. The need for a retap is almost nonexistent with the use of continuous guidance. Continuous ultrasonographic guidance is especially important with early amniocentesis. You need to be able to get adjacent to the amniotic membrane and then perform a sharp popping motion (through the amnion), rather than a steady motion, to avoid pushing the amniotic membranes to the posterior well of the uterus.

Dr. Allen, we have not had trouble with cell cultures. As you can see, the only failure we have had in this series was a situation in which I failed to obtain sufficient fluid. One of our fears when we first started doing early amniocentesis was culture failure because early amniotic fluid contains fewer viable cells. However, they seem to make up for their decreased numbers by growing more vigorously in tissue culture. In almost all cases we are able to get at least 15 clones and 5 karyotypes, which are the numbers the state recommends as the standard.

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Seventy-one quadruplet pregnancies: Management and outcome

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This article reviews the epidemiology, management, and outcome of 71 quadruplet pregnancies that occurred between 1980 and 1989. A study of detailed medical questionnaires and medical records revealed that 67 (94%) of the pregnancies followed ovulation induction therapy. A majority of the pregnancies were diagnosed by 9.3 weeks' gestation and bed rest was institutec by 16.7 weeks; 14% of women had cervical cerclages. Tocolytic agents were used in 59 (83%) of the group beginning at 24.5 weeks' gestation. The mean gestational age at delivery was 31.4 weeks and the mean birth weight was 1482 gm. Cesarean sections were performed in 89% of the cases. The average maternal weight gain was 45.8 pounds. Of the 284 fetuses, there were six first-trimester losses (including one ectopic pregnancy), 10 stillbirths and 33 neonatal deaths, resulting in a stillbrith rate of 29 per 1000, and corrected neonatal and perinatal mortality rates of 37 per 1000 and 67 per 1000, respectively. Other than premature labor, the most common maternal complications were first-trimester bleeding (35%), toxem a (32%), and anemia (25%). The quadruplet fetal growth curve parallels the singleton 25th percentile until 34 weeks, when it drops below the 10th percentile. These data suggest that a majority of quadruplets are delivered after 28 weeks and a viable outcome is expected. Because of retarded growth after 34 weeks, delivery should be considered at 34 weeks in most cases. (Am J Obstet Gynecol 1990;162:1384-92.)

Key words: Quadruplets, growth curve, complications, prematurity

Since the introduction of gonadotropin therapy in 1959 and clomiphene citrate (Clomid) in 1961 for ovulation induction, a major increase in multifetal pregnancies has occurred.[1-6] Hellin's rule for approximating multiple births is no longer applicable. Twins, triplets, and quadruplets exceed the 1 in 90, 1 in 90^2, and 1 in 90^3 predictions based on this hypothesis.[2] Multiple gestations occur in 6% to 8% of pregnancies induced by Clomid and 20% to 40% of those associated with gonadotropins, but most of these are twins. Quadruplets are reported in 0.3% of Clomid-induced pregnancies and 2.6% of gonadotropin-induced gestations.[1] The actual incidence of quadruplet gestations since the advent of modern reproductive technology is unknown. Quoted incidences range from 1 in 677,000[3] to 1 in 5370.[4] More importantly, information on perinatal outcomes for larger order gestations is scanty; thus counseling pregnant patients with supermultiples and planning their management is hampered.

A study of 71 quadruplet pregnancies was undertaken to survey pregnancy management and outcomes. The largest modern series of quadruplets reported six pregnancies.[4, 5] A recent review found 17 pregnancies discussed in a total of six papers.[6] Although still rare, quadruplets occur frequently enough that a review of a series this size is warranted to describe their natural history in the 1980s.

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6/6/19050

Material and methods

Detailed medical questionnaires were collected through The Triplet Connection, a support group for mothers of supermultiples. These surveys were designed by a physician advisory panel to accumulate data on triplet or greater pregnancies. The Triplet Connection is a nonprofit organization that collects and disseminates information on superfetal gestations. It works closely with an advisory panel, which includes perinatologists and obstetrician-gynecologists.

One hundred forty-two women with delivered and undelivered quadruplet pregnancies have contacted The Triplet Connection for information. Seventy-one of the 121 delivered pregnancies supplied adequate information through completed medical questionnaires, medical records, and hospital summaries and are the subject of this report. Fifty pregnancies were excluded because there was no questionnaire available. There were 17 fetal and neonatal losses in this group of excluded pregnancies. Sixty-three precent of the women established contact with the organization during pregnancy and were followed up on a prospective

basis. The following information was requested: patient age, gravity, parity, prenatal weight, total weight gain, timing of diagnosis, use of ovulation induction agents, and fertility procedures. Questions on prenatal management included the timing and length of bed rest; the use of tocolysis, steroids, cerclage, and home monitoring; the number and length of hospitalizations, and the prenatal complications. Information on timing and method of delivery, birth weight, neonatal course, and postpartum complications was obtained. A growth curve was derived from the birth weights from pregnancies without fetal losses. This curve was compared with a singleton growth curve.[7]

Results

A profile of the 69 patients who were delivered of 71 quadruplet pregnancies is reported in Table I. Mean maternal age was 29.3 years (range, 19 to 36 years); 41 patients were nulliparous. Multiple births had previously occurred in five of these women. There were two patients with twins and one with triplets. Two surveyed mothers reported two quadruplet pregnancies, all of which are included. The group had above-average education and income levels; 75% had college or postgraduate degrees; 76% had family incomes of >$30,000.

The 71 pregnancies were delivered in 27 states and two Canadian provinces. A higher number of respondents were from California (n = 9). Illinois (n = 6), Massachusetts (n = 5), Michigan (n = 5), and Indiana (n = 5). Most of the pregnancies were managed by perinatologists (69%) in level III units (86%). General obstetrician-gynecologists provided care for 30% of these pregnancies with perinatal consultation. Only 13% of the women were delivered in a level II facility.

Ovulation-inducing agents were used in 67 of 71 pregnancies (94%); only four quadruplet gestations were conceived spontaneously. Clomiphene as a single agent was associated with 15 pregnancies. Over half (n = 8) of these 15 occurred with the first course at a starting dose of 50 mg per day for 5 days.

A variety of gonadotropin regimens with combinations of Pergonal, menotropin, human chorionic gonadotropin, and Clomid caused 52 (73%) of the quadruplets; gamete intrafallopian transfer resulted in 18% (n = 13), and in vitro fertilization 7% (n = 5) of the multiples. The gonadotropin regimens alone, without egg retrieval techniques, accounted for 34 of the 52 gonadotropin-induced pregnancies.

In two of the four spontaneously conceived quadruplet pregnancies, identical siblings occurred. The only set of identical quadruplets were female and were delivered at 28 weeks. One of the four siblings died at 14 days of multiple anomalies. A biovular pregnancy, with three identical boys and one girl, was delivered at 34 weeks and all infants survived. The third spontaneously conceived quadruplet pregnancy was delivered of four fraternal girls. The fourth patient was hypothyroid and was delivered of three nonidentical girls and one boy at 26½ weeks. One neonatal death resulted from sepsis and respiratory distress syndrome.

Table I. Profile of 69 patients with 71 quadruplet pregnancies

Mean maternal age (yr)		29.3
Nulliparous (n = 41)		59%
Prior multiple pregnancies		5
College or postgraduate education		75%
Income >$30,000		76%
Ovulation induction		
Spontaneous	4	(6%)
Clomid (alone)	15	(21%)
Gonadotropin regimens	52	(73%)
Gamete intrafallopian transfer	13	(18%)
In vitro fertilization	5	(7%)

Chronologically, over half (n = 37) of the study group was delivered in 1988 or during the first 6 months of 1989 (Fig. 1). All gamete intrafallopian transfer and in vitro fertilization pregnancies were in this period. The broader application of ovulation-inducing agents and increased reporting to The Triplet Connection are logical explanations for this trend.

Important trends in management are noted from study of the accumulated data (Table II). Ultrasonography has played a valuable role in diagnosis and monitoring of growth and viability in these pregnancies. In all patients the diagnosis of supermultiples was made before delivery, although two pregnancies were misdiagnosed as triplets until delivery. The average timing of ultrasonographic diagnosis was 9.3 weeks (range, 4 to 32 weeks). Growth was closely monitored with an average of 11.2 ultrasonographic exams per pregnancy; a total of 790 exams were done in 70 pregnancies. Early bed rest is evidenced by the mean onset of partial or total bed rest at 16.7 weeks, with an average duration of 13.1 weeks (range, 4 to 24 weeks).

The mean maternal weight gain in 70 pregnancies was 45.8 pounds (range, 11 to 100 pounds). Patients answering questions on diet consumed between 1800 and 6000 calories per day with high protein levels. Dietary intake was a major problem in the first trimester with hyperemesis and after 26 weeks when extreme abdominal distention was notable. No significant correlation existed between maternal weight gain and newborn birth weight.

Ten patients underwent cerclage for premature cervical changes. Sutures were placed at 16.6 weeks' gestation for an average duration of 14.6 weeks. These patients were delivered at a mean gestational age of 31.2 weeks, which was not different from the noncerclage group.

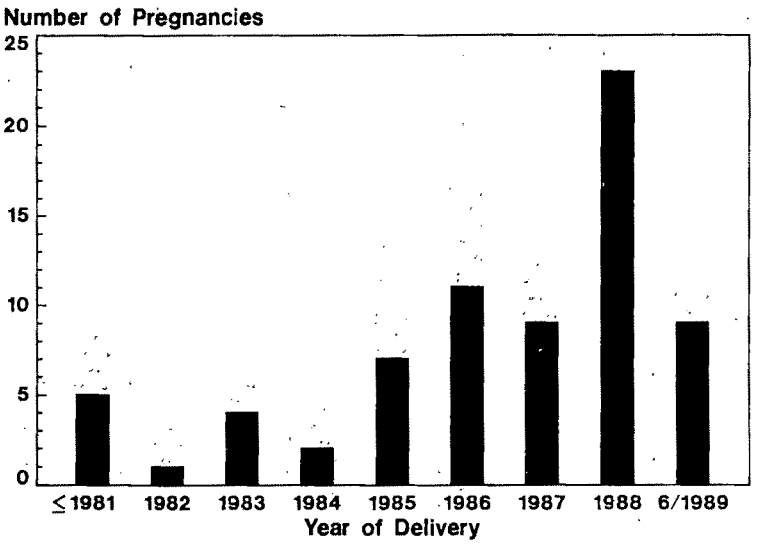


Fig. 1. Chronologic distribution of 71 quadruplet pregnancy deliveries.

Patients reported that home fetal monitoring (TOKOS) was helpful in differentiating contractions from excessive fetal movement. Home monitoring began in 1986. Twenty of 52 patients (38%) who were delivered since its availability have used this system either at home or in the hospital at bed rest.

Steroid therapy to enhance fetal lung maturity was used in 18% of pregnancies for periods of 1 to 8 weeks. In all cases, it was used on an inpatient basis when delivery appeared imminent. It had no obvious impact on mortality rates.

Tocolysis was used in 83% (n = 59) of pregnancies with the mean onset of premature labor at 24.5 weeks. It was difficult to differentiate between prophylactic and therapeutic use of tocolysis. Terbutaline, ritodrine, and magnesium sulfate were used singly or in combination. One half of the women were treated with terbutaline. Three patients were managed with the terbutaline mini-pump. Indomethacin and progesterone were used as supplemental therapy.

Hospital admission data were difficult to interpret. As expected, lengthy stays and frequent admissions were common. The most common complications necessitating admission were premature labor, toxemia, and bleeding.

The proper method of delivery for supermultiples is debated in the literature.[4,6] The trend in recent years has been to proceed with operative delivery; 89% of the pregnancies were delivered by cesarean section, 8% by vaginal delivery, and 3% by a combined vaginal and cesarean delivery.

Major prenatal complications included premature labor, first-trimester bleeding, incompetent cervix, pregnancy-induced hypertension, and anemia (Table III). Premature labor complicated 70 of 71 pregnancies. Its mean onset was 24.5 weeks (range, 20 weeks to term). The only pregnancy without premature contractions was delivered of three stillborn infants and one live infant at 38 weeks. Two other pregnancies were delivered after 37 weeks. One patient had been hospitalized for 24 weeks. The other had previously been delivered of triplets, had a cerclage, and remained at bed rest for 18 weeks. She was delivered by a third cesarean section at 38 weeks when the membranes ruptured.

First-trimester bleeding was reported in 25 pregnancies (35%). Four of five prenancies with a "vanishing fetus" (in which four living fetuses reduced to three) had early bleeding. Perinatal mortality, incidence of premature labor, and timing of delivery did not differ significantly for women with first-trimester bleeding. However, six of these patients experienced postpartum hemorrhage and four required transfusion.

It was determined from the questionnaire data that pregnancy-induced hypertension developed in 23 patients. Mean maternal age, delivery date, and bed rest for these women were not statistically different from the normotensive patients. Six of the 23 patients received steroids to enhance pulmonary maturity. All were admitted when pregnancy-induced hypertension was diagnosed. Seven neonatal deaths occurred in pregnancies complicated by preeclampsia and five of these seven were delivered at less than 29 weeks' gestation. Two mothers had pulmonary edema and congestive heart failure. Both had preexisting anemia and suffered postpartum hemorrhages. One had received betamethasone for 6 weeks before delivery.

In addition to the 10 cerclages mentioned earlier, surgical procedures included two salpingo-oophorectomies, one salpingectomy, and a pituitary tu-

Table II. Management of 71 quadruplet pregnancies

Early diagnosis	9.3 wk (Range, 4 to 32 wk)	
Serial ultrasonography	790/70 patients (Mean, 11.2 scans per pregnancy)	
Bed rest	Onset 16.7 wk (Duration 13.1 wk; range, 4 to 24 wk)	
Cerclage	10 patients (14%)	
Home monitoring	20 patients (38% since 1986)	
Mean weight gain	45.8 lbs (Range, 11 to 100 lbs)	
Premature labor	Onset 24.5 weeks (Range, 20 to 37 weeks)	
Steroids used	13	(18%)
Tocolysis	59	(83%)
Terbutaline (oral, subcutaneous, pump)	35	(49%)
Ritodrine	19	(27%)
Magnesium sulfate	13	(18%)
Indomethacin	3	(4%)
Progesterone	2	(3%)
Delivery		
Cesarean section	63	(89%)
Vaginal	6	(8%)
Combined	2	(3%)
Hospital		
Level III	61	(86%)
Level II	9	(8%)
Level I	1	(1%)
Physician		
Perinatologist	49	(69%)
Obstetrician-gynecologist	21	(30%)
Family practice	1	(1%)

Table III. Antenatal and postnatal complications of 71 quadruplet pregnancies

Complication	*n*	%
Premature labor	70	98
First-trimester bleeding	25	35
Pregnancy-induced hypertension	23	32
Anemia	18	25
Incompetent cervix	10	14
Urinary tract infection	10	14
Gestational diabetes (insulin dependent, 2)	7	10
Surgical procedures	4	6
Asthma	3	4
Renal stone	1	1
Prolapsed cord	2	3
Abruptio placentae	2	3
Postpartum hemorrhage	15	21
Transfusion	9	13
Postoperative incisional infection	3	4
Postoperative hematoma	2	3
Congestive heart failure and pulmonary edema	2	3
Thrombophlebitis	1	1

mor removal. The 10 cerclages were done at 16.6 weeks (range, 12 to 25 weeks) and helped maintain pregnancies until a mean delivery of 31.2 weeks (range, 28 to 38 weeks). Eight of 10 cerclage patients received tocolysis. Both salpingo-oophorectomies were done for ovarian hyperstimulation, which was complicated by a ruptured hemorrhagic cyst in one case and ovarian torsion in the other. The procedures were done at 18 and 20 weeks, respectively. A salpingectomy at 11 weeks' gestation was needed for a ruptured ectopic pregnancy. This patient subsequently had a cerclage placed at 20 weeks and was then delivered at 29 weeks. All neonates survived with minimal respiratory distress.

A patient whose first set of quadruplets died at 22 weeks underwent transsphenoidal removal of an enlarging prolactinoma. Surgery was performed at 20 weeks when medical therapy failed and visual loss progressed. Four healthy girls were delivered by cesarean section at 36 weeks.

Postpartum hemorrhage was reported in 21% ($n = 15$) of the surveyed mothers and 13% ($n = 9$) required transfusion. Excessive blood loss in two patients necessitated six 1-unit transfusions. Hemorrhages were caused by abruptio placentae in two cases and uterine atony in seven. One case of abruptio placentae at 20 weeks resulted in four neonatal deaths and the patient required curettage plus transfusion for retained products of conception. The other case occurred at 33 weeks, but all four infants survived. In addition to requiring transfusion, this mother had thrombophlebitis and received anticoagulant therapy for 4 months post partum. One patient with persistent postpartum bleeding caused by subinvolution of the uterus had curettage 3 weeks after delivery. The 15 pregnancies complicated by postpartum hemorrhage were delivered at a mean gestational age of 32.5 weeks and therefore had a total uterine volume that was comparable with the group that did not report excessive bleeding.

Outcome for these 71 pregnancies is outlined in Table IV. Although premature labor became evident at 24.5 weeks' gestation, delivery occurred an average of 7 weeks later, at 31.4 weeks ± 3.6 (mean ± SD). Delivery time ranged from 20 to 38 weeks' gestation. Fig. 2 demonstrates that most deliveries (67%) occurred after the 31.4 week mean, with clustering between 31 and 35 weeks. In fact, 73% of pregnancies were delivered after 30 weeks and 87% were delivered after 28 weeks.

Birth weight ranged from 255 to 2914 gm. The group mean was 1482 gm. This calculation excluded all first-trimester losses and stillbirths. A gender ratio of 1.3 to 1.0 existed, with 158 females and 118 males identified and reported. Sex was unknown in eight fetuses.

Graphing all birth weights at each gestational age allows some helpful observations (Fig. 3). Live births,

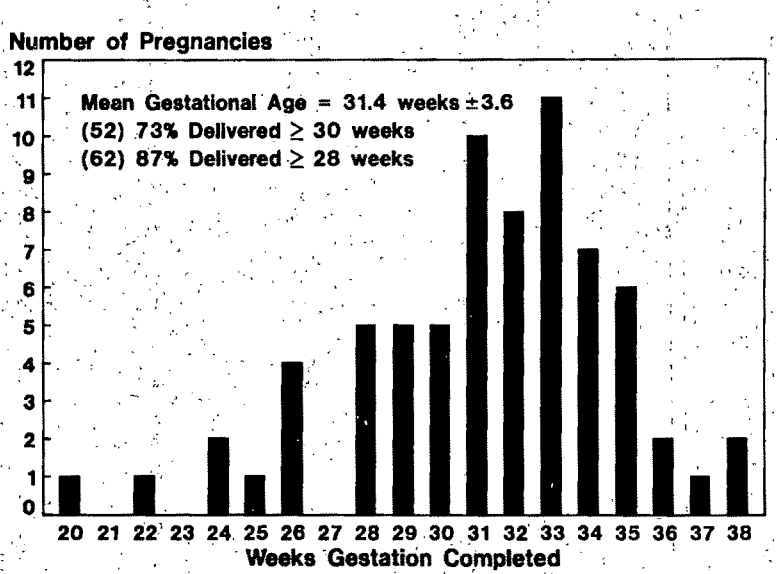


Fig. 2. Distribution of 71 quadruplet pregnancies by gestational age at delivery.

Table IV. Pregnancy outcome

Premature labor	Onset 24.5 wk (range, 20 to 37 wk)	
Gestational age at delivery	31.4 ± 3.6 wk (mean ± SD) (Range, 20-38 wk) 87% (n = 62) delivered >28 wk	
Mean birth weight	1482 gm (Range, 255 to 2919 gm)	
Fetal sex		
Male 118		
Female 158		
Unknown 8		
Pregnancy losses		
Missed abortions		5
Ectopic pregnancy		1
Stillbirths		10
Neonatal deaths		33
20-27 wk	24	
28-31 wk	8	
≥32 wk	1	
Sudden infant death syndrome (2½ mo, 4½ mo)		2

stillbirths, neonatal deaths, and missed abortions or vanishing fetuses are depicted by the symbols on the graph legend. Median birth weights were calculated after excluding pregnancies in which a stillbirth or missed abortion occurred. Therefore only pregnancies resulting in delivery of four living neonates were used in mean and median birth weight determination.

Of note were the concentration of neonatal deaths less than 28 weeks and the stillbirth occurrence after 32 weeks. "Vanishing fetuses," as mentioned earlier, were first-trimester missed abortions that had early ultrasonographically documented heart tones. The stillbirths along the baseline occurred months before delivery of the pregnancy and had no weight reported.

Fetal growth progressed in a linear fashion until 32 weeks when it slowed. By superimposing percentiles derived from singleton delivery data[7] and plotting the medians for quadruplets, this growth deceleration becomes more obvious (Fig. 4).

Less than 20% of quadruplet fetuses exceed the 50th percentile for singletons. Only six fetuses exceed the 75th percentile and most of these were delivered before 32 weeks. The "growth-retarded" fetuses (<10th percentile) dramatically increased at 34 weeks. Less than one fourth of the fetuses are below the 10th percentile before 34 weeks, whereas 62% are below that level after 34 weeks; χ^2 square analysis shows this difference is significant ($p < 0.001$).

Comparison of the quadruplet median birth weight curve with the singleton percentiles better illustrates this difference (Fig. 5). Growth approximates the 25th percentile for singletons until 34 weeks, when the quadruplet median birth weight drops below the 10th percentile for singletons. From 34 weeks until birth, the majority of quadruplet fetuses are "growth retarded" by singleton standards.

Fetal mortality consisted of one ectopic pregnancy, five vanishing fetuses or missed abortions, and 10 stillbirths. The six pregnancies with first-trimester losses all progressed normally to delivery between 31 and 35 weeks. In the missed abortions, four living fetuses spontaneously reduced to three with loss of heart activity in one fetus early in the pregnancy.

Table V details the 10 stillborn infants. Six died months before delivery and had no notable effect on the live-born siblings. Four fetuses died between 32 and

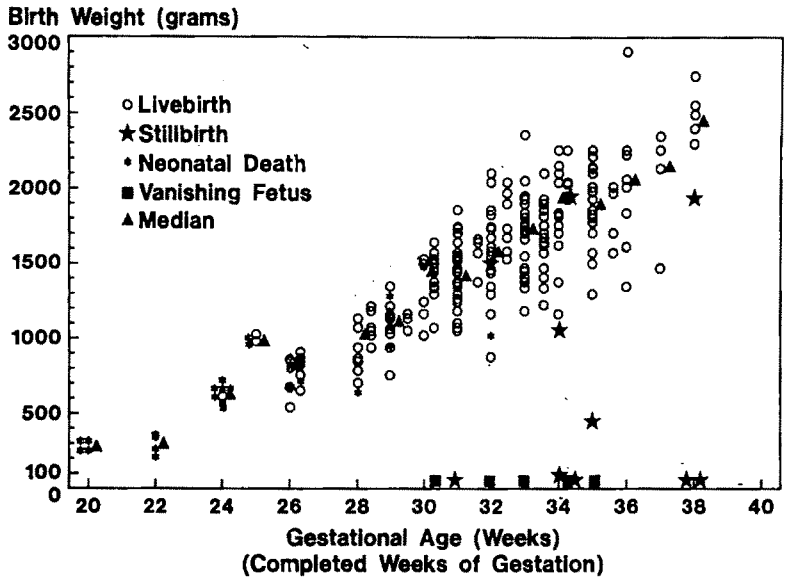


Fig. 3. Birth weights of 284 quadruplets arranged by gestational age and coded as live births (n = 235), neonatal deaths (n = 33), stillbirths (n = 10), or vanishing fetuses (n = 5). Median birth weights were calculated excluding pregnancies with any pregnancy loss.

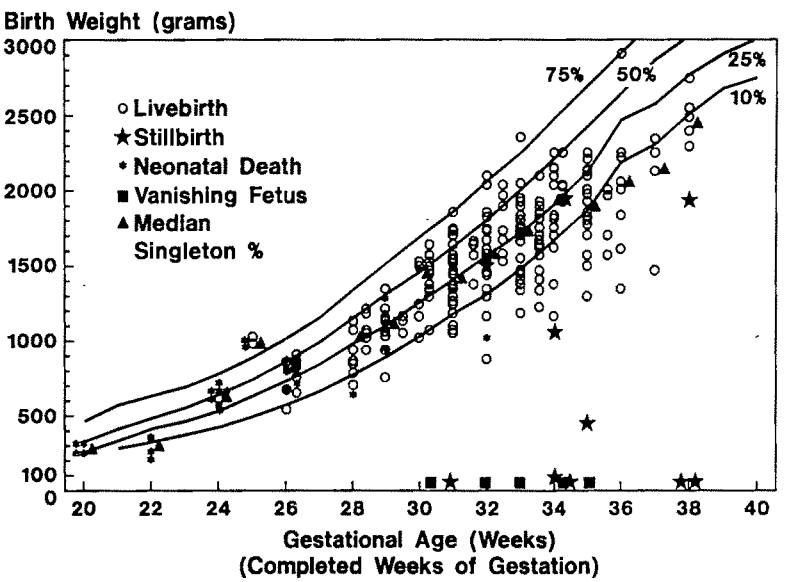


Fig. 4. Comparison of quadruplet birth weights with singleton percentiles for fetal weight.

38 weeks' gestation, within days of the delivery data. Of note were three intrauterine fetal deaths that occurred in a single pregnancy delivered at 38 weeks. Identical twins expired at 18 weeks and later, just before delivery, a fraternal sibling (1924 gm) died. Another pregnancy complicated by multiple stillbirths was delivered at 34 weeks. An unexplained fraternal 22-week loss preceded the 33½-week death of a markedly discordant identical twin. At birth the live twin weighed 1018 gm more than its stillborn counterpart. A mother with 12 weeks of bleeding, a history of smoking, and a previous pregnancy with intrauterine growth retardation had a stillbirth at 20 weeks. The remaining four fetal deaths are detailed in the table. Excluding the twin intrauterine fetal demises at 18 weeks as abortions, eight true stillbirths in 278 quadruplet fetuses yields a stillbirth rate of 29 per 1000.

Thirty-three neonatal deaths occurred in the 268 live births. Twenty-four infants who died during the neonatal period were delivered before 28 weeks' gestation and weighed under 1 kg. Eight were delivered between 28 and 30 weeks, with birth weights between 900 and

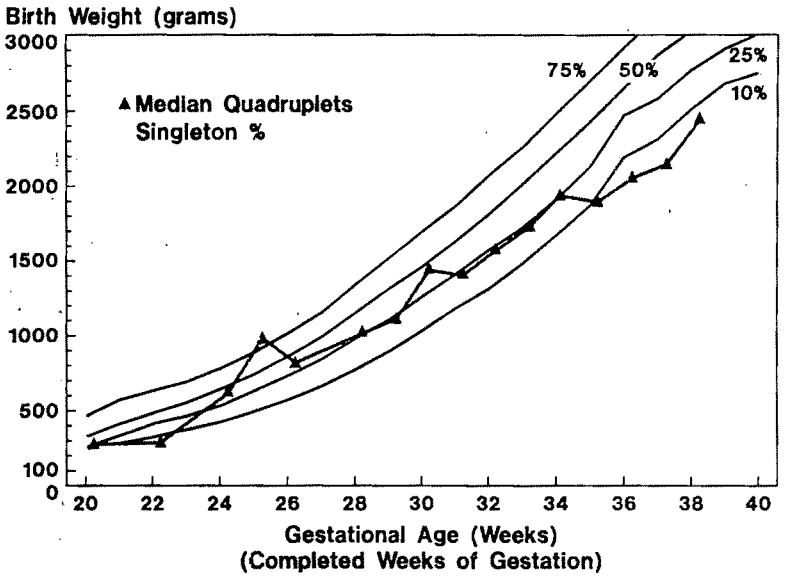


Fig. 5. Median quadruplet birth weights compared with percentiles for singleton birth weights.

Table V. Stillbirths

Delivery (wk)	*n*	*Details of death*
38	3	1 Pregnancy; identical twins died 18 wk, fraternal sibling died at 38 wk, 1924 gm
35	1	Intrauterine fetal death 20 wk, smoker, previous intrauterine growth retardation
34	2	1 Pregnancy; 22 wk intrauterine fetal death, 33 wk discordant identical twin (1047 vs 2065 gm)
34	1	Potter's syndrome
34	1	Cord accident, birth weight 1953 gm
32	1	Oligohydramnios
31	1	Neural tube defect—hydrocephalus

Table VI. Perinatal mortality

Stillbirth rate	29/1000
Neonatal mortality rate	123/1000
Corrected for <28 wk	37/1000
Perinatal mortality rate	147/1000
Corrected	67/1000

1400 gm. The latest neonatal death occurred at 32 weeks and the infant weighed 1000 gm at birth. The infant was significantly growth-retarded and died after a repair of a patent ductus arteriosus.

The neonatal mortality rate is 33 per 268 (123/1000). If newborn infants <28 weeks are excluded, the corrected neonatal mortality rate is 9 per 244 (37/1000). Three infants who died in the neonatal period weighed less than 1000 gm at birth but are included.

A perinatal mortality rate of 147 per 1000 (Table VI) is calculated if all losses before 20 weeks are included. The majority of losses are a result of severe prematurity (<28 weeks). By correcting for neonatal deaths that occurred before 28 weeks, a corrected perinatal mortality rate is 67 per 1000.

Sudden infant death syndrome occurred in two infants. The first was a growth-retarded boy delivered at 34 weeks. He weighed 1160 gm, 700 gm less than his nearest-sized sibling. Death occurred at 10 weeks of infancy, 6 weeks after hospital discharge. The second infant was a girl born at 31 weeks. She weighed 20 gm more than the mean sibling birth weight, was discharged 6 weeks after delivery, and died at 4½ months of age.

Comment

McKeown and Record[8] published outcome data of 27 quadruplet pregnancies that occurred between 1931 and 1951 in Britain. This had been the largest series to date. The average gestational age cited was 33.8 weeks and the mean fetal birth weight was 1394 gm. These figures are surprisingly close to the 31.4 weeks and 1482 gm we report for our series of 71 quadruplet pregnancies. The British series had a corrected perinatal mortality of 509 per 1000. This was significantly different from the 67 per 1000 reported here.

Criticism of methodology in our study is warranted. Two major limitations of the questionnaire format are (1) bad outcomes can select out, and (2) self reporting subjects data to reporting inaccuracy. Over 63% of patients have contacted The Triplet connection during their pregnancies; thus telephone follow-up is possible when questionnaires are not returned. The 50 delivered pregnancies excluded for lack of a questionnaire were known to have 17 losses in 200 fetuses or an un-

corrected perinatal mortality of 8.5 per 1000, which is better than the figure reported for the 71 studied pregnancies. Their inclusion would only lower the perinatal mortality.

The sample selection is biased because the study women had to contact The Triplet Connection and complete the detailed questionnaire to be included. They are motivated, well educated, and had better than average demographic characteristics. Over 90% of quadruplets result from state-of-the-art reproductive technology, which is sometimes only a possibility for these types of individuals. Hence preselection has occurred long before quadruplet conception does. The demographics of the group, it seems, would also enhance the accuracy and reliability of the self reporting.

Modern quadruplets are an iatrogenic phenomenon. Polyovulation was induced in 94% of this group. The margin between a hyperstimulatory dose and minimum effective dose of ovulatory stimulants is narrow; this has been described for gonadotropins[1] but not for clomiphene. It was surprising to find that eight of the 15 Clomid quadruplet conceptions occurred with the first treatment cycle and with a starting dose of 50 mg. The number of gamete intrafallopian transfer ($n = 13$) and in vitro fertilization ($n = 5$) quadruplet gestations in this group could, however, be reduced. With improved technology and cryopreservation, a more appropriate number of eggs or preembryos could be used.

If there is a natural history for the quadruplet pregnancy, one would profile the typical patient as being 29.3 years of age, nulliparous, well educated, with a better than average income, who used an ovulatory stimulant to conceive. Diagnosis of multiple pregnancy was generally made at 9 to 10 weeks and the pregnancy was followed very closely with serial ultrasonography. Bed rest began at 16 weeks. Premature labor occurred by 24 weeks and tocolysis was used. A weight gain of 46 pounds and a period of bed rest lasting 13 weeks could be anticipated. Delivery would be by cesarean section at 31 weeks in a level III hospital, with the patient cared for by a perinatologist. The mean quadruplet birth weight is 1482 gm. The risk for stillbirth begins around 32 weeks. The risk of neonatal death ends at about 28 weeks. There is a 93% chance of survival after the pregnancy reaches 28 weeks; over 85% of these pregnancies reached that mark.

In conclusion, a natural history of this multifetal gestation can be described with the data from 71 quadruplet pregnancies. The outcome was better than expected: 87% of pregnancies were delivered after 28 weeks. Corrected neonatal and perinatal mortality rates were 37 per 1000 and 67 per 1000. After 34 weeks, quadruplet fetal growth was retarded, intrauterine deaths increased, and no neonatal deaths occurred. Once that milestone is reached, delivery is a reasonable consideration should risks involved warrant it.

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Discussion

DR. JAMES J. M. MORAN, Santa Monica, California. I would like to compliment the authors on their excellent article on the modern management and outcome of quadruplet pregnancies in the United States. It was obviously the result of extensive and tedious field research.

Despite the inherent problems mentioned in this type of research, several problems in the successful management of these cases were noteworthy: a high incidence of premature labor, pregnancy-induced hypertension, and bleeding. It appears from their data that early bed rest, use of tocolytic agents, and frequent use of ultrasonographic examinations appear to be beneficial in the successful outcome of these cases. Of current interest is the use of home monitoring and home nonstress testing, which may be helpful and cost effective in the prevention of preterm delivery and avoidable stillbirth.

It would appear that the use of antenatal steroids, especially for extended periods of time, which has become more popular, may prove to be somewhat risky and must be carefully monitored.

The thorny ethical problem of selective termination of one or more fetuses in grand-multiple pregnancies entails problems never before encountered. Should we terminate some fetuses to save others, especially if the parents plan to abort the entire pregnancy to avoid the known hazards? How do we choose those to live and those to die? Evans et al.[1] discuss these ethical issues in a very thorough article. They had four cases of grand-multiple pregnancies managed by selective termination of all but two fetuses in each patient. Two pregnancies were successful in outcome, but the other two failed to bring any live fetuses to term. In fact, in one case one of the remaining twins had renal agenesis. Thus better and earlier diagnostic techniques are needed before one embarks on such a controversial course.

Since this is generally an iatrogenic disease,with only

6% being spontaneous occurrences, it would appear that prevention of this phenomenon would help to prevent the difficulties of premature labor, the necessity for prolonged bed rest, and the frightening ethical decisions mentioned above.

Finally, it is clear that successful management of these difficult pregnancies requires a team approach involving the patient, family, obstetrician and perinatologist, pediatrician and neonatologist, and ancillary services to provide careful monitoring and counseling in a home or hospital setting.

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Dr. Frank Terada, Honolulu, Hawaii. About 2½ years ago we started our in vitro fertilization program in Honolulu. Because the local insurance companies cover only one attempt, we have aimed for a very high level of stimulation with estradiols with doses up to 3000 pg/ml for most patients. In a few cases we had retrievals of 36 and 42 eggs; we do not have a freezing program yet. We have transferred as many as 12 embryos, and as a result we have had a higher number of multiple pregnancies. To date, we have had six quadruplet pregnancies; one started as a quintuplet and had a spontaneous vanishing fetus. All six patients have been sent to California for embryo reduction. Four have already been delivered of twins and two more are carrying twins at this time. All four carried their pregnancies almost to term; the last two pregnancies were carried until 37½ weeks with infants weighing approximately 6½ to 7 pounds each. All pregnancies were rather uncomplicated; one patient flew in from Maui every month for prenatal care. All were delivered by cesarean section, and problems were minimal.

Dr. Charles Plows, Anaheim, California. We thrive on anecdotes in this organization. I am going to tell you about delivering quadruplets 20 years ago in an 0.5 level hospital. The mother was 29 and had not taken any ovulation drug. Because she had no insurance, I did not hospitalize her but I made a house call practically every day during her last few weeks. The hospital, the pediatricians, my associates, and I donated all services. At the time of cesarean section, we tried to identify the placenta for each infant with various clamps on the cords. Of course, once we delivered the infants with all of these clamps, the circulating nurse promptly removed them all. We lost even that little bit of scientific information. We had no α-fetoprotein testing, no ultrasonographic scans, no fetal monitors, just a lot of luck. The patient carried the pregnancy to 37 weeks. According to the findings in this paper, we should have delivered her at 34 weeks. Three of the babies weighed over 4 pounds. The smallest weighed 2 pounds, 14 ounces and did not survive. This was a rather primitive episode by today's standards. Those boys are now 20 years old. I thought you would like to hear that quadruplets could be delivered in a very low level hospital with a reasonable degree of success.

Dr. Simon Henderson, San Francisco, California. When we treat patients with menopausal gonadotropins, we try to retrieve a reasonable number of eggs because our success rate in terms of pregnancies depends on that. This observation has also been made with in vitro fertilization and embryo transfer. Fortunately, only very rarely do all five or six eggs fertilize and implant in the uterus, but there is an increased chance of one or two doing so. Therefore we must realize that multiple pregnancy is a rather rare result of our treatment and that our success depends on producing very few of these multiple pregnancies. In this vein, I do not really see that by improving our ovulation protocols we are going to stop multiple pregnancies from occurring.

I think this is an encouraging study. The outcome of quadruple pregnancies has been extremely good, considering the circumstances. Referring to my own personal experience, I had one quadruplet pregnancy induced with Pergonal. The patient was hospitalized at 14 weeks and was delivered at 35 weeks. She had severe sciatica throughout this period. She did not have premature labor. The infants, all weighing about 4 pounds, were delivered by cesarean section and all did very well. The couple was fairly affluent and had four English nannies to care for the infants.

In light of the findings in this study, I think that we still need to determine whether we should advise patients with quadruplets to have selective termination or to continue their pregnancies. We should give these patients information from this study to help them make this decision.

Dr. Keith Russell, Los Angeles, California. Dr. Collins, I am curious about the one ectopic pregnancy. Were these a quadruple ectopic pregnancy, or one ectopic among four?

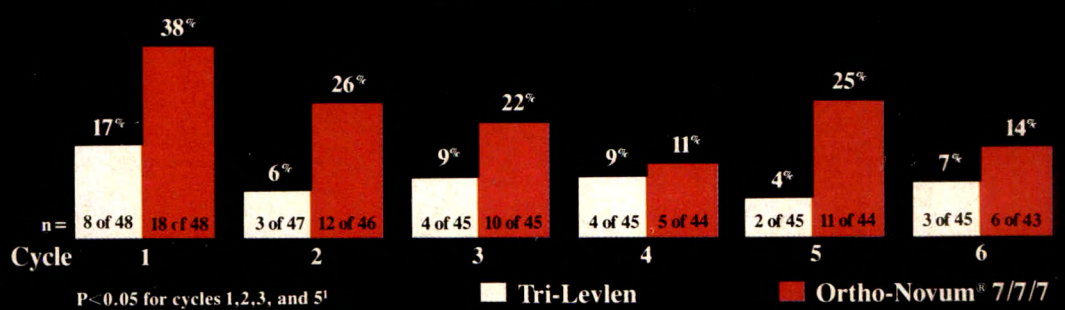
Dr. Kenneth Burry, Portland, Oregon. With patient surveys it is very easy to obtain biased data. Patients with good outcomes may respond and those with poor outcomes may not. Because a substantial number of your questionnaires were not returned, how much do you think your data are biased?

Dr. Collins (Closing). Dr. Russell, the ectopic pregnancy that involved one fetus ruptured at 11 weeks. The mother had cerclage at 20 weeks and was delivered of the other three infants at 29 weeks.

Reporting bias is a major limitation of any questionnaire study. Of the women who contacted this organization, however, 63% did so during pregnancy and could be followed up prospectively. The 50 patients who did not return questionnaires were called and follow-up was obtained. There were 50 losses among 200 fetuses, a perinatal mortality rate that is actually lower the one presented for the 71 study pregnancies. Excluding this group would not markedly affect the neonatal or perinatal mortality rates. The questionnaire format, although not ideal, was the most effective way to gather data on this number of quadruplet pregnancies.

Tri-Levlen® means a low incidence of breakthrough bleeding/spotting*†

Multicenter study demonstrates significantly less breakthrough bleeding/spotting through the first six cycles[1]



n = number of women with a bleeding event occurring during a cycle.

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Levonorgestrel and ethinyl estradiol tablets Triphasic regimen

may mean a lot to a woman

* Incidence defined as percentage of women with a bleeding event occurring at least once during a pill cycle. Serious as well as minor side effects have been reported with the use of oral contraceptives. The physician should remain alert to the earliest symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. Please see full prescribing information, a brief summary of which follows.

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BRIEF SUMMARY
Tri-Levlen®—6 brown tablets, each containing 0.050 mg of levonorgestrel (d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxy-gon-4-en-3-one), a totally synthetic progestogen, and 0.030 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol); 5 white tablets, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol; 10 light-yellow tablets, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol (7 light-green tablets containing inert ingredients are included in the 28-day triphasic regimen).

Indications and Usage—Tri-Levlen Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OCs) as a method of contraception.

Contraindications—OCs should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during the use of OCs or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of OCs is well established. Three principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OCs are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION—An increased risk of myocardial infarction associated with the use of OCs has been reported, confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an OC user or not. OCs, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in OCs. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the U.K. estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OCs according to age, smoking habits and duration of use. The overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking and duration of use, nor to compare the effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OCs) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OCs in women over 40 who smoke. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with OCs increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes or history of preeclamptic toxemia and, especially, by cigarette smoking. The physician and the patient should be alert to the earliest manifestations of thrombophlebitis and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four-to-six-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OCs should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Great Britain involving cerebrovascular disease and another study in the United States concerning myocardial infarction suggest that an increased risk of these conditions in users of OCs persists after discontinuation of the OC. In the British study, the risk of cerebrovascular disease remained elevated in former OC users for at least six years after discontinuation. In the U.S. study, an increased risk of myocardial infarction persisted for at least 9 years in women 40- to 49-years-old who had used OCs for five or more years. The findings in both these studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions:* There have been reports of neuro-ocular lesions, such as optic neuritis or retinal thrombosis, associated with the use of OCs. Discontinue OC medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma:* Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina and liver. Certain synthetic progestogens, none currently contained in OCs, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case-control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OCs. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time OCs were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only OCs. Several studies have found no increase in breast cancer in women taking OCs or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with OCs, found an excess risk in the subgroups of OC users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of OCs has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with OCs. Close clinical surveillance of all women taking OCs is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use OCs.

4. *Hepatic Tumors:* Benign hepatic adenomas have been found to be associated with the use of OCs. One study showed that OC formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of OCs. Two studies relate risk with duration of use of OCs, the risk being much greater after 4 or more years of OC use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking OCs. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring and Malignancy in Female Offspring:* The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence at the present time that OCs further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OCs. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including OCs, in pregnancy. One case-control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OCs, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OCs. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OCs is unknown. recommended that, for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing. patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first mi period and further use of OCs should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient shou apprised of the potential risks to the fetus, and the advisability of continuation of the pregnancy should be discussed in the lig these risks. It is also recommended that women who discontinue OCs with the intent of becoming pregnant use an alternate for contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no pr information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estr combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease:* Studies report an increased risk of surgically confirmed gallbladder disease in users of OCs and estrogen one study, an increased risk appeared after 2 years of use and doubled after 4 or 5 years of use. In one of the other studies increased risk was apparent between 6 and 12 months of use.

7. *Carbohydrate and Lipid Metabolic Effects:* A decrease in glucose tolerance has been observed in a significant percentag patients on OCs. For this reason, prediabetic and diabetic patients should be carefully observed while receiving OCs. An increas triglycerides and total phospholipids has been observed in patients receiving OCs. Three studies have been performed with the Levlen Tablets (Levonorgestrel and Ethinyl Estradiol Tablets Triphasic Regimen) formulation and no significant alterations in metabolism were noted, with the exception of a slight increase in triglyceride levels in one study. The clinical significance of t findings remains to be defined.

8. *Elevated Blood Pressure:* An increase in blood pressure has been reported in patients receiving OCs. In some women, hyperten may occur within a few months of beginning OC use. In the first year of use, the prevalence of women with hypertension is low in u and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer expos and in the fifth year of use is two-and-a-half to three times the reported prevalence in the first year. Age is also strongly correlated the development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more like develop elevation of blood pressure when given OCs. Hypertension that develops as a result of taking OCs usually returns to nor after discontinuing the drug.

9. *Headache:* The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persisten severe, requires discontinuation of OCs and evaluation of the cause.

10. *Bleeding Irregularities:* Breakthrough bleeding, spotting and amenorrhea are frequent reasons for patients discontinuing OCs breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changin an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necess since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhe young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuatio OCs. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive metho Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding:* OCs given in the postpartum period may interfere with lactation. There may be a decrease in the quantity quality of the breast milk. Furthermore, a small fraction of the hormonal agents in OCs has been identified in the milk of moth receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of OCs should deferred until the infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OCs. The pretreatm and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic orga including Papanicolaou smear and relevant laboratory tests. As a general rule, OCs should not be prescribed for longer than 1 y without another physical examination and PAP smear being performed. 2. Under the influence of estrogen-progestogen preparatio preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed a the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking OCs sho stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. OCs may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patie with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice wh receiving OC therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Sten hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in su patients. 7. OC users may have disturbances in normal tryptophan metabolism whi may result in a relative pyridoxine deficiency. The clinical significance of this is yet to determined. 8. Serum folate levels may be depressed by OC therapy. Since the pregna woman is predisposed to the development of folate deficiency and the incidence of fola deficiency increases with increasing gestation, it is possible that if a woman becom pregnant shortly after stopping OCs, she may have a greater chance of developing fola deficiency and complications attributed to this deficiency. 9. The pathologist should advised of OC therapy when relevant specimens are submitted. 10. Certain endocrin and liver-function tests and blood components may be affected by estrogen-containi OCs: a. Increased sulfobromophthalein retention. b. Increased prothrombin and facto VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platel aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circula ing total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or T4 by radioimmunoassay. Free T3 resin upta is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced respon to metyrapone test.

Information for the Patient—See Patient Package Labeling

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracyclin

Carcinogenesis—See "Warnings" section for information on the carcinogenic potential of OCs.

Pregnancy—Pregnancy Category X. See "Contraindications" and "Warnings."

Nursing Mothers—See "Warnings."

Adverse Reactions—An increased risk of the following serious adverse reactions has been associated with the use of OCs (se "Warnings"): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertensior gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of OCs, although additional confirmatory studies ar needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving OCs and are believed to be drug-related: Nausea and/o vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms (such as abdomina cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and afte treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes tenderness, enlargement and secretion; change in cervical erosion and cervical secretion; possible diminution in lactation when give immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses The following adverse reactions have been reported in users of OCs, and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, ner vousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis porphyria, hemolytic uremic syndrome.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OCs by young children Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration—To achieve maximum contraceptive effectiveness, Tri-Levlen Tablets (Levonorgestrel and Ethinyl Estradio Tablets—Triphasic Regimen) must be taken exactly as directed and at intervals not exceeding 24 hours. (If Tri-Levlen is first taker later than the first day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on it unti after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.) Any time the patient misses 1 or 2 brown, white or light-yellow tablets, she should also use another method o contraception until she has taken a tablet daily for 7 consecutive days.

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Breast cancer detection: Experience in a suburban community

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Six hundred sixty-nine breast biopsies performed at the Methodist Hospital of Southern California and the Arcadia Outpatient Surgery Center during 1987 and 1988 were reviewed. Three hundred twenty-eight biopsies were performed for clinical indications (lump, thickening, or nipple discharge). Three hundred forty-one biopsies (51%) were peformed because of mammographic abnormalities, and required preoperative x-ray localization. Of the 341 localized biopsy specimens, 261 were varieties of fibrocystic mastopathy, fibroadenoma, papilloma, or hyperplasia. An additional 31 cases showed atypical ductal or lobular hyperplasia. One hundred fifty-one breast cancers were detected in this series of 669 breast biopsies. One hundred two (68%) of these were detected as a result of a clinical finding, and 49 were detected as a result of mammographic abnormalities (a 32% incidence of occult breast cancers). Among the 341 x-ray localization biopsies performed, breast cancer was detected in 14%. (AM J OBSTET GYNECOL 1990;162:1393-7.)

Key words: Breast biopsies, mammography, breast cancer, occult breast cancer

Breast cancer is the most common cancer in women[1] and is the leading cause of death from cancer in women age 40 through 49 years.[2] Because early detection dramatically improves long-term survival,[3] the ability to diagnose this disease at an early stage is vital. Increased public awareness and widespread use of mammography have contributed to our ability to diagnose breast cancer earlier. The gradual reduction in radiation exposure to the breast with both film and xeromammography has resulted in more liberal use of screening mammography. Radiation dosage to the breast (expressed as mean glandular dose) is now approximately 0.04 R per film with film screen technique.[4] With the increased use of mammography in breast screening and improved quality, an increasing number of breast cancers are being detected in a nonpalpable stage.

This article reports the retrospective analysis of breast biopsies performed at a suburban community hospital and a freestanding outpatient surgical center during 1987 and 1988.

Material and methods

To ascertain the effectiveness of breast cancer screening in the Arcadia, California community, breast biopsies performed at Methodist Hospital and the Arcadia Outpatient Surgery Center during the years 1987 and 1988 were reviewed. Review of this biopsy material does not include all cases of breast cancer diagnosed in the local area because some patients with abnormal mammograms or clinical findings were referred to centers outside the local area for microscopic diagnosis and definitive treatment. Analysis of this material, however, yields a reasonable indication of the effectiveness of breast cancer screening in this community.

At both the Arcadia Outpatient Surgery Center and the Methodist Hospital of Southern California, biopsies were performed on the basis of clinical findings (lump, thickening, nipple discharge) or mammographic abnormalities. Xeromammography was used more commonly than plain film mammography in this community. Biopsies were performed by general surgeons (n = 18), family practitioners (n = 3), and gynecologists (n = 2).

Biopsies were performed with patients under either general or local anesthesia, depending on the preference of the patient or surgeon and on the clinical situation; often the patient preferred a one-stage frozen section followed by immediate definitive surgical treatment if cancer was found. Suspicious breast lesions detected by mammography were needle localized radiographically and a small amount of methylene blue was injected into the abnormal area. All dye-stained tissue was excised at biopsy. Frozen section or specimen radiography was performed to confirm that the significant radiographic abnormality had indeed been excised.

Results

Table I demonstrates an overall summary of the results of 669 biopsies. Results of 151 breast biopsies revealed cancer; 49 of these lesions were detected by mammography alone and thus were clinically occult (32%).

The age range for patients diagnosed with breast

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6/6/19907

Table I. Summary of results

Biopsies	669
Breast cancers	151
Occult breast cancers	49 (32%)
Atypical hyperplasias	31
Mammography-generated biopsies	341 (51%)
Percentage of breast cancers in localized biopsies (49/341)	14%
Percentage of breast cancer and atypical hyperplasia in localized biopsies (80/341)	23%

Table II. Age of patient with breast cancer at time of diagnosis

Age group (yr)	*No.*	*%*
30-39	7	5.0
40-49	15	10.0
50-59	29	19.2
60-69	47	31.1
70-79	34	22.5
80-89	17	11.2
90-99	2	1.0

cancer was from 32 to 92 years. The largest number of cancers occurred in the 60 to 69-year-old group. There were 47 cancers (31%) in this age group. Table II shows the incidence of cancer in various age groups.

There was a significantly higher incidence of cancer (27%) in the hospital-performed biopsies compared with a 16% incidence of cancer in the biopsies performed in the Arcadia Outpatient Surgery Center (Table III). This difference presumably represents the surgeons' selection of the hospital environment for biopsy in obvious clinically suspicious lesions when an immediate biopsy, frozen section, and mastectomy sequence might be preferred.

Benign disease was detected in 518 of the 669 biopsy specimens (77%). Included in this category were fibrocystic mastopathy, adenosis, fibroadenoma, papilloma, lipoma, and lobular, and ductal hyperplasia. An important subgroup of benign lesions includes the atypical hyperplasias, both ductal and lobular.

Three hundred forty-one of the 669 biopsies (51%) had preoperative radiographic needle localizations. Forty-nine of the 341 localized lesions were malignant (14%), and if the cases of atypical hyperplasia (31 cases) are included, the incidence of malignant or potentially malignant disease among localization-biopsy procedures is 23% (Table I).

Mammographically localized lesions were categorized as clustered calcifications, mass or asymmetric density, and spiculated mass. Table IV shows the radiographic features of the 49 occult or nonpalpable breast cancers detected in this survey. Clustered calcifications were the most common mammographic finding in these nonpalpable cancers.

Comment

The 32% incidence of clinically occult disease in the Arcadia Breast Cancer Survey is similar to that reported for the Breast Cancer Demonstration Detection Program (BCDDP).[3] It would appear that mammography is detecting approximately one third of breast cancers with current technology, indeed, an important observation.

In this series slightly more than half of the breast biopsies (341 of 669, or 51%) were performed as a result of mammographic abnormality. These 341 radiographic localization procedures resulted in the detection of 49 occult cancers, (14%), compared with reports of 14%, 16%, 29%, and 31% reported in the recent literature.[5-9] The relatively low yield of positive biopsy specimens in this series may have resulted from the nonuniform radiographic facilities, primary care physicians, and surgeons composing this study compared with higher percentage rates reported from more controlled studies in university-type environments.[9] The burden placed on the clinician, radiologist, and patient when a mammographic abnormality is detected is obvious. Only an aggressive approach to biopsy will detect breast cancer early. With the current state of technology, mammography may not always reliably differentiate between benign and malignant lesions.[6] Moskowitz[10] considers a 10% yield of malignancies from radiographically localized biopsies to be acceptable to avoid missing early breast cancer.

Of the localized biopsies, there were 31 in which either ductal or lobular atypical hyperplasia was diagnosed. The addition of these cases of atypical hyperplasia to the 49 occult carcinomas yields a 23% positive rate of malignant or potentially malignant biopsy results. The importance of atypical hyperplasia is emphasized by Page's study[11] showing the subsequent risk of invasive cancer to be four to five times that of the general population in a 17-year follow-up of cases of atypical hyperplasia.

In this series there were four palpable cancers not seen on the mammogram. (Unfortunately, the overall false-negative rate in this study cannot be determined because review of several records in which presence of a lump resulted in biopsy does not indicate that a mammogram was done). A negative mammographic result should not delay biopsy in those patients with a palpable lump or dominant mass, thickening, bloody nipple discharge, or other significant clinical signs because the false-negative rate for mammography may approximate 10%.[12]

No attempt was made to evaluate staging and treat-

ment in this study because a significant number of patients were referred to other treatment centers for definitive surgery, radiation, or chemotherapy. The impressive number of occult or nonpalpable breast cancers detected in this series lends credence to the importance of screening mammography.

The value of screening programs is evidenced by recent analysis of Breast Cancer Demonstration Detection Program data showing 87% and 81% 5- and 8-year survival rates, respectively, for all invasive breast cancers compared with an unscreened group with 74% and 65% rates, respectively, for those cases diagnosed in the National Center Institute Surveillance, Epidemiology and End Results programs. As expected, the highest survival rate occurred in those cases of occult breast cancer detected by mammography only (94%, 8-year survival).[3]

Clinicians should not be lulled into a false sense of security by the fact that the breast cancer was nonpalpable, because the incidence of positive axillary lymph node involvement has been reported as high as 34% in these minimal but invasive breast cancers.[13] However, a small cancer undoubtedly is better than a large one. If mammography results in detection of noninvasive cancers, the 10-year survival rate has been reported to be 100%.[14]

Considering that the doubling time for breast cancer cells may average 100 days, it would require 10 years for a tumor to attain a clinically palpable size of 1 cm.[15] In women with large breasts and a deep tumor, even a 1 cm tumor would be difficult to detect through palpation alone.

Moskowitz[10] estimates that with aggressively performed screening, a mean detection lead time of 2½ to 3½ years may be gained over the usual clinical detection of breast cancer. A recent comparison of palpable and nonpalpable breast cancers by Pagana et al.[16] found that the nonpalpable tumor was more often noninvasive, smaller, and nodal metastasis significantly less frequent. However, the frequency of nodal metastasis was similar when adjusted for size and grade.

If progress in reducing mortality in breast cancer is to continue, it is obvious that clinicians must urge more widespread use of mammography and implement screening recommendations advised by the American Cancer Society. Despite the overwhelming evidence supporting the use of mammography, over 60% of women older than age 50 have not had a mammogram in their lifetime.[17]

The gynecologist's role as a primary care physician in urging patients to perform breast self-examination, obtain a yearly breast examination, and have periodic mammograms is paramount. It behooves the clinican to become very involved in mammographic screening to assure his patients of good quality studies. It is highly desirable for the clinician to review all abnormal mammograms with the radiologist before management decisions with the patient.

Table III. Comparison of biopsies at Methodist Hospital and Arcadia Outpatient Surgery Center

	No.
Biopsies	
Methodist Hospital	371
Arcadia Outpatient Surgery Center	298
Breast cancers	
Methodist Hospital	102 (27% of biopsies)
Arcadia Outpatient Surgery Center	49 (16% of biopsies)
Occult cancers	
Methodist Hospital	31 (30%)
Arcadia Outpatient Surgery Center	18 (37%)

Table IV. Mammographic features of occult malignant lesions

Total occult lesions	*No.*	*%*
Clustered calcifications	20	41
Spiculated mass	12	24
Mass, density, or asymmetric density	17	35
TOTAL	49	100

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. James D. Fearl, Portland, Oregon. Dr. Goodno retrospectively reviewed 2 years of breast biopsy results at a general hospital and an outpatient surgery center in Arcadia, California. Breast lesions were identified about half the time by clinical findings and half by mammographic localization. Confirmation of mammographically identified lesions was done by frozen section or specimen x-ray film. One hundred fifty-one cancers were diagnosed from 669 biopsies. About one third of the cancers were occult lesions identified by mammographic criteria. These 49 occult cancers represented 14% of the 341 localized lesions. If the additional 31 atypical hyperplasias were added to the occult cancers, the total incidence of localization-biopsy procedures was 23%. Clustered calcifications were the most common characterization of nonpalpable lesions.

An apparent goal of this retrospective analysis was to ascertain the effectiveness of breast cancer screening in a local community. To accurately determine the effectiveness would, I think require working through the radiology departments to find the total number of mammograms performed and the number of biopsy specimens obtained elsewhere, as well as at the two institutions studied. The fact that 328 biopsies, which included 102 detected cancers, were done for clinical indications could suggest that mammography was underutilized, since it is not reported how many of these women had prior mammograms.

Although the benign/malignant ratio of 14:100 in this study falls above the stated minimum standard of 1:10, according to Moskowitz,[1] others feel 2:5 is the generally accepted ratio and as high as 1:3 is attainable.[2] The clinical criteria of thickening is likely to have many different meanings to 23 clinicians. I was unable to tell if mammograms were ever used or how often they were used to clarify the indication for biopsy in equivocal clinical findings. I believe the radiographic description of clustered calcifications can also have liberal interpretation. The high incidence of this finding was noted in the occult malignancies but not mentioned in the benign biopsy specimens.

Dr. Goodno, could you give the age distribution of the seven patients in the 30- to 39-year-old group? Were these patients screened for a risk factor or did they have biopsies because of clinical findings? To phrase this question in a politically acceptable way, do you think there was significant variation in interpretation criteria of the involved radiologists? To quote one of your references regarding decision to biopsy, the purpose is to obtain ". . . accurate radiologic criteria for biopsy without a plethora of unnecessary biopsies for suspicious mammographic findings."

Since completing your review and analysis, have you made any major changes in your general attitude toward breast screening or method of evaluating clinical breast findings?

During the last decade, the improvement in mammographic techniques and the increasing popularity of screening mammograms have been significant, but much controversy still remains. Considerable difficulty is described in correlating atypical hyperplasia and mammographic findings.[3] The frequent tendency for multicentric ductal hyperplasia makes mammographically directed biopsies difficult to correlate with mammographic findings. Unfortunately, medicolegal influence has great impact on screening and diagnostic criteria. A wide range of philosophies regarding screening mammograms are described in the literature. Moskowitz[1] thinks excessive claims for accuracy and sensitivity and specificity, particularly in screening, must be avoided. Humphrey and Ballard[4] describe the attributes of a good screening test to include high sensitivity and specificity. Marchant, in discussing breast cancer detection, questions whether sensitivity and specificity have any real meaning, sensitivity being an acquired art and specificity being irrelevant because ". . . when it's high, it's too late."[5]

Numerous studies show improved survival with early detection of breast cancer; however, as shown in the most recent national statistics, there does not appear to be a significant improvement in survival when national age-adjusted cancer death rates are examined.[6] Dr. Goodno quotes a reference that points out that more than 60% of women over age 50 have not even had a mammogram. That same reference mentioned the results of a survey that pointed out that the reason a high proportion of women had not had a mammogram was because their physicians had not recommended one to them. For a screening test to be worthwhile, the disease being screened for, and the screening test itself obviously must have certain characteristics such as low-cost, detectable preclinical phase, and a treatment for the disease must be more effective when applied to screening-detected disease than when applied to the symptom-detected disease. Nevertheless, the early detection efforts must have the enthusiastic support of physicians and be readily accepted by women.

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DR. WILLIAM HINDLE, Los Angeles, California. I note that half the biopsies were done because of mammography alone. The management of nonpalpable breast lesions is an entirely new field with which all gynecologists should become familiar. Mammographic accuracy depends on the number of cases seen and the skill of the radiologist reading the films. At the large breast centers in Sweden like the Karolinska Hospital in Stockholm, or similar centers in Falun, Goteborg, and Malmo, the accuracy is excellent. Dr. Tabar in Falun reads 300 mammograms a day (Tabar L. Personal communication, Falun, Sweden, 1989). This amounts to a total of 1200 films, two views for each side. His true-positive rate for the detection of nonpalpable cancer is 90%. In fact, if his pathologist does not find cancer, Dr. Tabar tells him to cut more slides because he "knows" that the cancer is there. In contrast, the minimum true-positive rate accepted by the American College of Radiologists is 10%. That is, of 10 nonpalpable lesions called "probably malignant" on the basis of mammography, one should actually prove to be a cancer. Most U.S. centers report around one cancer per five biopsies.

When we discuss palpable breast lesions, the woman's age becomes critically important. In a recent report of women who had palpable breast masses, Edeiken[1] found that 43% of the cancers were missed by mammography in women under 50 years of age. In women over 50 years, only 12% of lesions were missed by mammography. This is because fat displaces the glandular tissue and there is more mammographic contrast as women grow older. With the denser breasts of younger women, mammographic interpretation is more difficult.

I hope that in the future mammographers here, as in Sweden, will adopt the following interpretations of breast lesions: (1) mammographically malignant, (2) mammographically benign, or (3) mammographically indeterminate. The indeterminate lesions require open biopsy for definitive diagnosis. Swedish physicians have become so accurate with the use of fine-needle aspiration of breast lesions that they now do few open biopsies for diagnosis.

Dr. Goodno, were the in situ cancers included in the "malignancies" in the data you presented? It is unfortunate that the stage of the cancers could not be tabulated. The crux of all of this effort is the ultimate clinical outcome. Given the indolent, insidious nature of breast cancer, it may take more than 20 years to determine the final outcome.

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DR. GAINER PILLSBURY, Long Beach, California. One of the major dilemmas for clinicians who use screening mammography is the report of equivocal or suspicious radiographic findings in the absence of a palpable lesion. To improve accuracy and to diminish the number of unnecessary biopsies, we established a breast evaluation center in the spring of 1988 at Long Beach Memorial Hospital. We have a radiologist on site who reads only mammograms, and use dedicated mammographic equipment capable of magnification, and ultrasonographic equipment to differentiate solid from cystic lesions. We also have well-trained technologists. Between June 1, 1988, and Aug. 15, 1989, we performed 9428 screening mammograms. The films are batch read to reduce the cost. Patients with films that are interpreted as definitely positive have biopsies done. Many patients whose initial films are suspicious or equivocal are scheduled to return for additional studies, including magnification views, ultrasonography, or both. Tissue was obtained in 143 women after these procedures. Of these, 67 lesions were malignant and 76 were benign, a true-positive rate of 47%. These preliminary data support the concept that the use of enhanced imaging techniques and ultrasonography can reduce the incidence of false-positive mammograms and the number of unnecessary biopsies.

DR. ROBERT LOWDEN, Seattle, Washington. I would like to reiterate the statement that you should not trust the radiologist's report of a negative mammogram if you have a palpable mass. It is better to do a biopsy of the lump because otherwise you are going to miss a cancer. A big problem now with litigation is breast cancer missed by a gynecologist.

DR. GOODNO (Closing). Dr. Fearl, we do not have data about the number of screening mammograms performed to yield these mammographic abnormalities. I wish we did. We probably could obtain data concerning the 30- to 39-year-old women but I did not include such data in the study. Most of those lesions were actually palpable lumps rather than radiographic abnormalities. Like Dr. Pillsbury's hospital, we have also established a breast imaging center in Arcadia, which started in July of 1989. The center provides screening films and xerography and ultrasonography for complete evaluation of radiographic abnormalities. Dr. Hindle, in situ carcinomas were included in this study. We did not analyze staging or therapy because many of the patients with cancers identified in this study were referred to other centers—City of Hope, University of California, Los Angeles, Norris Tumor Institute, etc.—for definitive surgery, radiation, or chemotherapy.

Vaginal birth after cesarean or repeat cesarean section: Medical risks or social realities?

E. Paul Kirk, MD, Kathleen A. Doyle, MD, Janet Leigh, MD, and Mary L. Garrard, MSN
Portland, Oregon

Despite the known medical safety and success of vaginal birth after cesarean section, rates of planned repeat cesarean sections remain high. The process involved in women's decisions to choose vaginal birth after cesarean section or repeat cesarean section was investigated by a questionnaire study at a private and a public hospital. Women were questioned regarding timing, influence of others, reasons for their choice, satisfaction with the decision, etc. Results from 160 respondents showed that over half the women identified themselves as the primary decision maker. Physicians exerted more influence on the decisions of patients at the public hospital than on the patients at the private hospital. Overall, social exigencies appeared to play a more important role than an assessment of the medical risks in making these decisions. (AM J OBSTET GYNECOL 1990;162:1398-405.)

Key words: Vaginal birth after cesarean, repeat cesarean section, decision making, informed consent

The obstetric revolution of the last two decades has been characterized by the remarkable results in neonatal intensive care units, particularly with low-birth-weight infants, the development of the specialty of perinatology with the focus on the fetus as the patient, and new imaging and monitoring equipment to sharpen that focus, and the dramatically increased use of cesarean section as a method of delivery. Features of the revolution have included the virtual elimination of birth trauma and intrapartum fetal asphyxia death, decreasing maternal and perinatal mortality, decreasing morbidity from cesarean section, rising health care costs and, inevitably, an increasing number of women who enter the second pregnancy with the physical scars and the mental memories of the previous pregnancy, labor, and delivery.

As this revolution progressed, another revolution was occurring as pregnant women and their advocates in the late 1960s and early 1970s sought to gain more control over their pregnancies. They were anxious to move away from what was seen as the older paternalistic style, often typified by rigid labor practices, standing orders, spinal anesthetics, and elective outlet forceps. The new style was to include more patient autonomy, more flexibility, more expectant management, fewer physical interventions, more effective childbirth preparation, fewer narcotics, and the encouragement of the delivery as a family event with early mother-infant interaction in the neonatal period.

By the late 1970s the trend of the rising cesarean section rate was established and proponents were forecasting a continuing progressive rise.[1] Skeptics doubted that there was any direct relationship between the increased use of cesarean sections and improved perinatal outcome. Experts were called together to halt this trend and to proffer some sound advice regarding the management of abnormal, and therefore difficult labor and the diagnosis of fetal distress. They cautiously suggested that vaginal delivery after a previous transverse, low-segment cesarean section might be safe under certain rigidly controlled conditions.[2] This cautious opinion was based on the limited information available at that time, which implied that these vaginal deliveries carried a much lower risk to mother and fetus than had been assumed by the practice based on Craigin's original threatening dictum: "Once a section—always a section."

The last decade has seen an accumulation of experience and data that fully support the consensus recommendation and studies have shown that the risk of uterine rupture is low.[3-6] Consequently, the risk of fetal injury from uterine rupture is very low and importantly, the probability of vaginal delivery is high: 75% to 80% in those women who attempt vaginal birth after cesarean section. More recent studies have responded to some of the previously unanswered questions regarding the safety of vaginal births after cesarean sections with Pitocin administration, epidural anesthetics,[7] low vertical incisions,[8] "unknown" scars,[9] multiple pregnancies,[10] and breech presentations.[11] As the data have

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Table I. Reasons for women's choice of vaginal birth after cesarean section (percentage)

	*All factors**		*Single most important factor†*	
	Hospital A (n = 70)	*Hospital B (n = 41)*	*Hospital A (n = 70)*	*Hospital B (n = 41)*
Danger of cesarean section for mother	23	41	0	0
Danger of cesarean section for infant	20	29	0	0
Longer recovery with cesarean section	61	89	21	44
Wanted experience of vaginal birth	61	66	19	27
"Naturalness" of vaginal birth	—	—	17	12
Financial considerations	3	7	0	2
Other	20	18	43	15

*Identified from a checklist.

†Identified by an open-ended question.

accumulated, public statements have been less cautious. A recent American College of Obstetricians and Gynecologists committee recommended that "The concept of routine repeat cesarean birth should be replaced by a specific indication for a subsequent abdominal delivery, and in the absence of a contraindication, a woman with one previous cesarean delivery with a low transverse incision should be counseled and encouraged to attempt labor in her current pregnancy."[12] It would seem that these good results would correspond with the more autonomous style of management of a subsequent pregnancy and that the prospects of a safe delivery, with a good probability of avoiding another abdominal incision, would be enticing.

The national experience does not support this assumption. A recent survey published in 1987 showed that 92% of women with a history of previous cesarean sections are delivered by repeat elective surgery and in 50% of the nation's hospitals, a vaginal birth after cesarean section has never been attempted.[13]

It is not clear who makes the decision to avoid vaginal births after cesarean section, and why those decisions are made when the clinical data now available would support a much more optimistic approach. In an attempt to understand some of the issues in this clinical management decision, a questionnaire study was undertaken.

Material and methods

The study was conducted at two hospitals in the Portland, Oregon metropolitan area: University Hospital (hospital A) and Good Samaritan Hospital (hospital B). Questionnaires were issued to all patients who were delivered of infants between Dec. 1, 1988, and June 30, 1989, who had a history of cesarean section in any of their previous pregnancies. The questionnaires were issued during the postpartum hospital stay; if they were not completed by the time the patient was discharged, one further attempt was made by mail at a later time to have the questionnaire completed. The questionnaires were designed to describe the ethnic and educational characteristics of the different hospital populations. Separate questionnaires were used for those patients who planned a vaginal birth after cesarean section and for those who chose repeat cesarean section. The questions attempted to identify the patient's perceptions with regard to the management decision and the factors that affected that decision. The answers were collated and comparisons were made between hospital A and hospital B, and between those who chose vaginal birth after cesarean section and those who chose repeat cesarean section.

Results

Two hundred fifty-seven questionnaires were distributed; 160 (62%) were returned. Patients planning a vaginal birth after cesarean section at hospital B were more likely to return the questionnaire (73%) than the repeat cesarean section group (47%) (overall return rate from hospital B, 59%). The return rates for vaginal birth after cesarean section and repeat cesarean section groups were virtually identical at hospital A (66% versus 61%); the overall return rate was 65%. At hospital A there was a total of 1480 births with 265 cesarean sections; the cesarean section rate was 17.8% (14.8% primary, 3% repeat). At hospital B there were 1245 births; the cesarean section rate was 19%, (13.6% primary, 5.4% repeat).

The average age of the patient with a vaginal birth after cesarean section was 27.6 years (range, 17 to 41 years), and for the repeat cesarean section group, 30.6 years (range, 18 to 42 years). Ninety-one percent were married or identified a steady partner. Hospital B respondents tended to have a higher educational level, with 69% of hospital B versus 47% of hospital A patients having some college or a college degree; 19% and 5% of hospital B and hospital A patients, respectively, had a professional degree. Eighty percent of patients from hospital A were white; the remainder came from a variety of minority backgrounds. All but one patient from hospital B were white.

Eighty-four percent of patients at hospital A had had their prenatal care at a resident or county clinic, with only half attending for their first prenatal visit in the

Table II. Time women reported first hearing about vaginal birth after cesarean section (percentage)

	Women planning vaginal birth after cesarean section			*Women planning repeat cesarean*		
	Hospital A (n = 70)	*Hospital B (n = 40)*	*Both (n = 110)*	*Hospital A (n = 16)*	*Hospital B (n = 33)*	*Both (n = 49)*
Never heard about vaginal birth after cesarean section	3	0	2	19	3	8
Before current pregnancy	49	65	55	38	55	49
First half of current pregnancy	26	30	27	12	30	24
Last half of current pregnancy	10	3	7	12	3	6
During labor	6	0	4	0	0	0

Table III. Timing of decision for vaginal birth after cesarean section or repeat cesarean (percentage)

	Women planning vaginal birth after cesarean section			*Women planning repeat cesarean*		
	Hospital A (n = 70)	*Hospital B (n = 41)*	*Both (n = 110)*	*Hospital A (n = 15)*	*Hospital B (n = 33)*	*Both (n = 48)*
Before current pregnancy	23	37	28	27	9	15
First half of current pregnancy	33	54	40	27	24	25
Last half of current pregnancy	26	7	19	20	58	46
During labor	9	0	5	13	6	8

Table IV. Reasons for choice of repeat cesarean section (percentage)

	Women planning repeat cesarean		
	Hospital A (n = 15)	*Hospital B (n = 33)*	*Both (n = 48)*
Danger of vaginal birth after cesarean section for mother	33	21	25
Danger of vaginal birth after cesarean section for infant	20	33	29
Avoid pain of labor	20	49	40
Convenience of timing birth	13	33	27
Low probability of vaginal delivery	33	61	52
Knew what to expect	27	42	38

first trimester. At hospital B, 95% of the prenatal care was in a private office, and 90% of the first visits were in the first trimester.

The responses to the question regarding reasons women chose vaginal birth after cesarean section are summarized in Table I. Half the patients were aware of vaginal birth after cesarean section as an option before conception (Table II). The patients from hospital A had no clear pattern in the timing of the decision, whereas patients at hospital B tended to make the decision for vaginal birth after cesarean section early in pregnancy and for repeat cesarean section, late in pregnancy (Table III).

The patient's reason(s) for choosing an elective repeat cesarean section are listed in Table IV. The patient's perceptions of her chances of vaginal delivery are shown in Table V. The majority of patients identified themselves as the decision maker either alone (55%) or in conjunction with the physician (34%), although the physician alone was identified as the decision maker in 11% of hospital A vaginal births after cesarean sections, and 33% of hospital A repeat cesarean sections (Table VI). The patient's perceptions of the physician's attitude toward vaginal birth after cesarean section are listed in Table VII. Even though the patient perceived herself as being the primary decision maker, 64% and 46%, respectively, identified the physician and the husband or partner as having "a lot" of influence on the decision. "Others" (friends, parents, siblings, nurses, childbirth educators) were more likely to influence the decision when a vaginal birth after cesarean section was chosen. This difference was more obvious with patients from hospital A (Table VIII); physician influence was stronger at hospital A than at hospital B: 69% of patients at hospital A versus 59% of patients at hospital B stated their physicians had "a lot" of influence. In the 25 patients who had a repeat cesarean section after a failed vaginal birth after cesarean section, 52% were for management of failure to progress and 40% were for management of fetal distress. Of those 25, 48% said that they would never try vaginal birth after cesarean section again, whereas 20% said that they would definitely try again. Only 27% of patients planning a vaginal birth after cesarean section and 20% of repeat cesarean section patients attended a prenatal class. Patients from hospital B were more

Table V. Women's perceptions of their chance to deliver vaginally (percentage)

	Women planning vaginal birth after cesarean section			*Women planning repeat cesarean*		
	Hospital A (n = 69)	*Hospital B (n = 41)*	*Both (n = 110)*	*Hospital A (n = 16)*	*Hospital B (n = 33)*	*Both (n = 49)*
Poor (<25%)	23	12	19	50	49	49
Fair (25% to 50%)	19	22	20	19	24	22
Good (75%)	38	51	43	12	12	12
Excellent (>90%)	20	15	18	6	9	8
Unaware of vaginal birth after cesarean section as option	0	0	0	13	6	8

Table VI. Women's perception of who made the decision for vaginal birth after cesarean section or repeat cesarean section (percentage)

	Women planning vaginal birth after cesarean section			*Women planning repeat cesarean*		
	Hospital A (n = 70)	*Hospital B (n = 41)*	*Both (n = 111)*	*Hospital A (n = 15)*	*Hospital B (n = 33)*	*Both (n = 48)*
Self	53	61	56	33	61	52
Physician	11	2	8	33	3	13
Both	36	36	35	27	33	31
Other	6	0	4	7	3	4

likely to attend prenatal classes than those from hospital A (34% vs 17%).

Comment

Although there has been extensive discussion of the lack of necessity to perform a repeat cesarean section in the light of the proven safety of vaginal birth after cesarean section, only 8% of women in the nationwide survey underwent a trial of labor in 1984. The likelihood of a trial increased with the size of the obstetric service, and it is likely that some of the reluctance to permit a trial may be related to the availability of emergency services, although it is important to note that other intrapartum catastrophes occur more frequently than uterine rupture.[14]

Even on larger obstetric services, the rates of vaginal birth after cesarean section did not exceed 25%, and there is uncertainty whether this is because the physicians do not allow trials of labor, or that mothers do not want to experience them. Within the admitted limitations of a questionnaire study, some patterns appear to emerge. Both hospitals in the study have a relatively low cesarean section rate by modern standards, and each promotes vaginal birth after cesarean section. The population in hospital B is almost exclusively white, better educated, and receives prenatal care early through private physician offices. At hospital A, the population is ethnically heterogeneous, is less well educated, and is likely to receive prenatal care later from a variety of providers in different settings, most of whom would not provide longitudinal care through delivery. In general, women from hospital B gave better defined opinions (Table IV), and the *troika* of the patient, partner, and physician seemed more important (Table VI). They tended to make the decision for vaginal birth after cesarean section earlier in the pregnancy but left the decision for a repeat cesarean section later. Both groups were reasonably well informed about vaginal birth after cesarean section, but their information was not always accurate. The women who chose repeat cesarean section were particularly pessimistic about their chances of a vaginal delivery, which was almost certainly a factor in the management decision. The patients from hospital A, who were relying on the physician, were more likely to receive information and support from other health care providers, family, and friends. The better educated group did not appear more interested in or more likely to choose vaginal birth after cesarean section, as has been previously reported by McClain.[15] The reasons for choosing vaginal birth after cesarean section (recovery period, wanting the experience) and for choosing repeat cesarean section (knowing what to expect, avoiding the pain of labor, convenience, and timing) confirmed the social rather than the medical model of the decision making. The exception to this was "the belief that the chance of vaginal delivery was poor," which is a misappreciation of the medical probability rather than an appreciation.

Although there are extensive reports in the literature

Table VII. Women's perception of physician's attitude toward vaginal birth after cesarean section (percentage)

	Women planning vaginal birth after cesarean section			*Women planning repeat cesarean*		
	Hospital A (n = 70)	*Hospital B (n = 40)*	*Both (n = 110)*	*Hospital A (n = 16)*	*Hospital B (n = 33)*	*Both (n = 49)*
Encouraged vaginal birth after cesarean section	74	95	82	31	24	26
Discouraged vaginal birth after cesarean section	0	0	0	25	21	22
Neutral	10	10	10	19	52	41
Don't know	16	0	10	25	3	10

Table VIII. Women's perception of amount of influence by "others" on decision for vaginal birth after cesarean section or repeat cesarean as "some" or "a lot" (percentage)

"Others" influencing decision	*Women choosing vaginal birth after cesarean section (n = variable)*	*Women choosing repeat cesarean (n = variable)*
Friends	47	15
Doctor	86	79
Nurse	61	24
Childbirth educator	40	13
Husband-partner	81	72
Parent(s)	43	21
Siblings	29	5

that analyze the factors that affect the cesarean section rates in various settings,[16, 17] and various descriptions of policy that have successfully reduced the cesarean section rates,[18, 19] there is little information about the decision-making process in individual cases. Through a series of structured interviews of 100 patients, McClain[15] emphasized that all women made choices that were shaped by social exigencies and constraints, and that none engaged in probabilistic evaluation of medical risk, choosing instead to develop negotiation strategies that would enhance control of uncertainties, such as the length and pain of labor.

In this study, although the physicians were identified as an important part of the decision-making process, patients in hospital A were not always able to identify what the physicians' attitudes were, possibly because of the lack of longitudinal care. Clearly, decisions are made either in favor of vaginal birth after cesarean section or repeat cesarean section, and this study raises questions about the nature of informed consent.[20] Ten years ago when vaginal birth after cesarean section was considered unsafe and 98% of women had repeat cesarean sections on the basis of the physician's concern for the risks of uterine rupture, the consent was, in a sense, uninformed because it reflected old data. It now appears that many women choose repeat cesarean section, an equally uninformed choice when assessed from the point of view of medical risk, but one that makes social sense because it respects individual preference. It appears that physicians are likely to collude with this choice, perhaps out of respect for patient autonomy, a reluctance to change long-held positions, a wish to avoid a failed vaginal birth after cesarean section in up to 25% of cases, or fear of litigation.

It is not possible to determine how well patients were informed in this study, nor how free was their consent. Seventy-three percent of patients who had a repeat cesarean section reported that their physicians either discouraged vaginal birth after cesarean section or had either neutral or unknown attitudes, although 26% chose to have a repeat cesarean section despite the physician's encouragement of vaginal birth after cesarean section. This in turn raises the question: Should the decision be simply the choice of the patient, a truly elective repeat cesarean section? By means of a mathematic probabilistic model, Feldman and Freeman[21] made a cogent argument for the consideration of prophylactic cesarean section at term in all pregnancies. An essential part of that argument was the significantly reduced maternal risk of elective cesarean section. Coupled with the lack of any convincing evidence that properly consented elective cesarean sections cause any prolonged postpartum depression or maternal infant interaction difficulties, the elective cesarean section appears to be a reasonable choice.

Two ethical considerations remain. First, how far should the obstetric community control individual decisions within the context of increasing costs, limited resources, widespread pregnancy indigency, and managed health care programs? It is clear that clinicians do not practice in a vacuum; whenever a decision is made to perform a cesarean section, it affects the total pattern of obstetric practice, which in turn affects the standard of care. Second, should the patient be free to make a choice for repeat cesarean section? If it is reasonable for her to make that choice in the setting under discussion, then it is neither reasonable nor logical to deny that choice to a woman who does not have a history of a previous cesarean section.

Obstetricians are concerned with balancing freedom

of individual decision making by the patient, with a desire to avoid unnecessary cesarean sections. Truly informed consent can only be provided when the patients understand the medical probabilities, and the physicians understand the social influences and the stepwise process that most patients appear to use in making a decision regarding a vaginal birth after cesarean section or a repeat cesarean section.

It may be that our understanding of the social issues would improve if the counseling commenced in the immediate postpartum period after the *primary* cesarean section. Perhaps parenting classes could be used to "debrief" patients and their families; physicians who are better informed about the patient's social reasoning would feel more confident in negotiating a management that pays more attention to medical probability.

There are obvious drawbacks to this type of study. The conclusions have not been submitted to detailed statistical analysis because of the 62% return rate on the original questionnaires. The described perceptions and trends in the responses would suggest that although the physician has a central role in the decision-making process, we have yet not found a successful way to advocate vaginal birth after cesarean section as we have for vaginal delivery in many other clinical settings.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. JAMES C. CAILLOUETTE, Pasadena, California. The author has contributed to a large body of literature published during the last decade on the subject of vaginal birth after cesarean section. Despite continued recommendations in support of vaginal birth after cesarean section, the rate of cesarean sections has increased. To better understand the dynamics of this issue, a search of the literature was conducted. What we may be surprised to learn is that obstetricians are *not* searching for ways to avoid a cesarean section, rather they are looking for reasons *for* doing a cesarean section. The following data support this presumption.

The World Health Organization has estimated that approximately 500,000 women die each year from pregnancy-related causes.[1] More than 98% of these deaths occur in developing countries where vaginal delivery is the rule. Maternal mortality rates in these countries are as much as 100 times higher than those in industrialized countries. The stated most common causes of death are obstructed labor and ruptured uterus, postpartum hemorrhage, eclampsia, infection, and complications of illegal abortion.

In a review article in 1987, Petitti[2] stated that, "Beginning in 1969 and continuing through 1983 there was a sharp decline in fetal mortality. Starting in 1969, the positive factors have been family planning, availability of abortion, Medicaid, neonatal intensive care units, electronic fetal monitoring and finally the rising cesarean section rate."

In 1988 the late John Figgs Jewett coauthored a paper entitled "Cesarean section-related maternal mortality in Massachusetts from 1954 to 1985."[3] The paper reports that "The cesarean section delivery rate in-

creased from about 5% in 1954 to 23% in 1984. From 1976 to 1984 the rate of maternal deaths directly related to cesareans section delivery remained essentially unchanged at 5.8/100,000 cesareans as compared to 10.8 maternal deaths per 100,000 vaginal deliveries." This is clear evidence supporting the safety of cesarean section over vaginal delivery in contemporary obstetrics.

To further understand the mind-set of today's obstetricians, a few medical-legal facts should be considered. In a National Institutes of Health publication on cesarean childbirth published in 1980, the subject of litigation was considered.[4] The report states that "Ninety percent of all obstetrical malpractice cases fall into two categories: failure to perform a cesarean delivery and improper use of forceps during delivery."

A recent issue of *Time* magazine on the subject of doctors and patients reported that "In 1988, for the first time in more than a decade, medical malpractice suits abated. Claims settlements were down $100 million from the 1987 high of $4.2 billion."[5] I am concerned that those who discuss the economics of vaginal birth after cesarean section never discuss the economics of litigation. The article further stated that "Nearly one quarter of all U.S. births are currently by cesarean section, which can be less risky to the baby than vaginal delivery and makes the doctor less vulnerable in court." When a popular weekly magazine expresses such a clear view of cesarean delivery, is it so difficult to understand the mind-set of today's obstetricians?

If reasonable people can agree that malpractice litigation is based on the presumption of a bad outcome, and if it is reasonable to agree that physicians strive for a good outcome, then safe medical practice becomes the issue.

This returns us to the issue of vaginal birth after cesarean section. The literature is filled with articles stating that vaginal birth after cesarean section is safe, successful in many cases and should be encouraged, yet it is still not embraced.

In a 1988 article titled, "A successful program to lower the cesarean-section rates," the program was not as successful as stated.[6] Myers and Gleicher[6] reported a 6.25% fetal mortality rate among 48 infants who were breech deliveries with vaginal birth after cesarean section, a sixfold increase over the national average of 1.06%. In addition, their 5-minute Apgar scores below 7 increased significantly from 3.0% to 4.9%, clearly not a success for vaginal birth after cesarean section.

After considering Dr. Kirk's paper, which encourages an increased attempt at vaginal birth after cesarean section, let us consider a different philosophy. Feldman and Freiman[7] have contributed a thought-provoking article titled "Prophylactic cesarean section at term."[7] The authors explored a number of questions asked by a plaintiff's lawyer. The final question was: "Don't you think a mother has the right to assume the extra risks of cesarean section for the sake of her unborn if she wishes to?" After citing many of the risks of vaginal delivery, the authors concluded with four important questions: "In the light of all these considerations, is it tenable for us to continue to fail to inform patients explicitly of the very real risks associated with the passive anticipation of vaginal delivery after fetal maturity has been reached? If an informed patient opts for prophylactic cesarean section at term, can it be denied? If a patient considers the procedure and decides against it, must she then be required to sign a consent form for the attempt at vaginal delivery? Has something important been overlooked?"

I began my resident training at LAC/USC Medical Center 34 years ago. There were 12 obstetrics-gynecology residents, and only a volunteer clinical attending staff. We delivered approximately 1000 infants each month and our cesarean section rate was less than 4%. I regret not performing a cesarean in more cases that it is comfortable for me to recall. Valuable lessons were learned at the great expense of patient health and safety. These are lessons that few residents today have occasion to learn. During my training and after 30 years in private practice, I cannot recall a single cesarean that I regret having performed. However, there have been a number of occasions when I regretted a vaginal delivery.

With clear evidence that the increase in cesarean sections has resulted in improved outcome, and since vaginal birth after cesarean section is associated with the risk of a bad outcome, would the author address the following questions? First, is the increase in the cesarean section rate in industrialized countries an attempt to achieve the perfect outcome? And second, since university hospitals and private hospitals have different populations and different outcomes, is not the difference of opinion and practice between academicians and clinicians to be expected?

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Dr. Leroy Casperson, Portland, Oregon. I went back to the archives after I saw this article in the program. My first patient with a vaginal birth after cesarean section was in 1963. From that time I have generally given the patient the option of a vaginal delivery or a repeat cesarean section. I have no statistics, but I have been impressed by how frequently the vaginally deliv-

ered baby was larger than the baby previously delivered by cesarean section for "cephalopelvic disproportion." The current terminology, *failure to progress*, is more accurate and an improvement.

When things go well for a long period, we can become blasé over possible complications that we have been warned to anticipate. The admonitions against induction, augmentation, use of epidural anesthesia, etc. are now frequently ignored. We treat many of these women like any other multiparous patient. Approximately 6 weeks ago I cared for a patient of my associate. Her first delivery was by cesarean section because of herpes. Her surgery and recovery were uncomplicated. She entered the hospital at term in early labor and was given an epidural and Pitocin augmentation after many hours of slow progress. At a 2+ station, after a failed manual rotation, I applied Kielland's forceps but was not able to rotate from right occipitoposterior presentation nor affect descent. I decided to do a cesarean section. When the peritoneum was opened, I saw flecks of meconium floating beneath and edematous vesicouterine plica. Beneath this was a total dehiscence of the previous transverse scar with the shoulder partially extruding. With difficulty, I could reach my hand alongside the head to disengage it. A 10 pound, 13 ounce girl with Apgar scores of 3 and 9 was then delivered. There was a T-shaped vertical extension toward the cervix, which I may have created manually because of the extreme thinness of the lower segment. The defects were repaired and she recovered uneventfully. In retrospect, I could identify two episodes of variable decelerations about the time of complete dilatation and the patient said she felt a sharp pain in the right lower quadrant then. Only these two events suggest when the rupture might have occurred.

Dr. Robert Goodlin, Denver, Colorado. The term vaginal birth after cesarean section was coined in Denver and vaginal births after cesarean sections are popular. In 1989 we had six cases in which the fetus was extruded through the uterine defect. The mothers were all in labor and all had low transverse scars. In two cases in which the patients had epidural anesthesia, the only sign of this problem was severe fetal distress. We wonder now if we should not return to having an operating room available for cases of vaginal birth after cesarean section. That was the case 25 years ago, but we have moved away from this idea. However, in both cases in our hospital, the house officers delivered the fetus within 6 minutes and the infants had good Apgar scores and cord pHs. I do think that we have been too casual about the problem of uterine rupture in vaginal birth after cesarean section.

Dr. Kirk (Closing). Dr. Caillouette, maternal mortality in underdeveloped countries is not the issue here. Cesarean sections are badly needed in underdeveloped countries; they do not have proper access to cesarean section. The issue is not decision making or indications for cesarean sections, it is access. I think this is one of the few topics that we cannot learn from medicine in underdeveloped countries. Your comments about Dr. Meyers' paper, I think, are fair but I will point out with respect that Dr. Meyers' three breech infants who were lost were all in mothers without uterine scars. Their paper introduced a system for critical evaluation of all indications of cesarean sections. Those three breech deaths raise questions about the management of breech presentations, but not about vaginal birth after cesarean section.

Of course, Dr. Goodlin, there is a risk involved with uterine ruptures whenever there is a scar in the uterus. I emphasized that it is important to keep that risk in perspective and I think we have not done this. We have tended to overemphasize the risk of uterine rupture but underemphasize the other risks that exist in difficult labors—cord prolapse, placentae abruptio, fetal distress, and difficult deliveries. I asked questions about indicated cesarean sections. What are the indications for repeat cesarean section and what are the social influences that are affecting these decisions?

Dr. Caillouette asked two questions: Are we in search of perfection? Are the university hospitals and the private hospitals different? The answer to the first question is yes, but we are far from reaching it and we are being ingenuous if we think we will find perfection by being uncritical about the indications for cesarean section. With regard to the second question, our patient populations are different, but surely clinical judgment and intellectual curiosity are prerequisites for both the community and the academic obstetrician.

I think we could learn from Inspector Clousseau of the Pink Panther movies that it is important to ask the right question and to ask it in the right way. You may recall that when Inspector Clousseau went into an inn and saw a dog lying on the floor, he said to the innkeeper "Monsieur, does your dog bite?" The innkeeper said "No." So Inspector Clousseau went up and patted the dog. The dog immediately bit him. Indignantly, Inspector Clousseau said, "But you said your dog didn't bite." And the innkeeper of course said, "Monsieur, that is not *my* dog."

Stage IA_2 squamous carcinoma of the cervix: Difficult diagnosis and therapeutic dilemma

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The International Federation of Gynecology and Obstetrics instituted a change in the classification for carcinoma of the cervix with a new substage IA_2. The criteria for this substage exceed the generally accepted criteria for microinvasion. Fifty patients with early invasive squamous cell carcinoma of the cervix were treated from 1976 through 1983 with a cone biopsy followed by a radical hysterectomy and pelvic lymph node dissection. These patients were reviewed to evaluate the ability to make the histologic diagnosis and to examine the natural history of the disease with maximal treatment. Histologically positive margins were found at the time of cone biopsy in 66% (33/50) of the patients. Negative margins at the time of cone biopsy were identified in 34% (17/50) of the patients. Residual invasive disease at the time of radical hysterectomy was found in 24% (4/17) of the patients with negative margins. Two of the 50 patients had positive lymph nodes. Three patients had recurrent metastatic disease. This study demonstrates that a preoperative diagnosis of stage IA_2 invasive squamous cell carcinoma of the cervix is a difficult diagnosis to establish and creates a therapeutic dilemma regarding treatment. (Am J Obstet Gynecol 1990;132:1406-11.)

Key words: Stage IA_2 squamous carcinoma of cervix, microinvasion

The concept of microinvasive carcinoma of the cervix as a distinct clinical entity was introduced in 1947.[1] The International Federation of Gynecology and Obstetrics (FIGO) in 1961 defined stage IA carcinoma of the cervix as early stromal invasion. In the early 1970s FIGO defined stage IA as microinvasive carcinoma but failed to provide guidelines for establishing the histologic diagnosis. In 1974 the Society of Gynecologic Oncology (SGO) provided the working definition: a microinvasive lesion is one in which neoplastic epithelium invades the stroma in one or more places to a depth of 3 mm or less below the base of the epithelium, and in which lymphatic or blood vessel involvement is not demonstrated. These histologic criteria have been generally accepted in the United States.

The Oncology Committtee of the FIGO recently mandated changes in the definition of stage IA carcinoma of the cervix.[2] Stage IA carcinoma of the cervix is subdivided into stage IA_1 and stage IA_2. Stage IA_1 is defined as minimally microscopically evident stromal invasion. This includes only those patients with minute foci of invasion visible only microscopically and not penetrating more than 1 mm below the basement membrane. Stage IA_2 is defined as lesions detected microscopically that can be measured. The upper limit of measurement must not exceed a depth of invasion of more than 5 mm taken from the basement membrane, either surface or glandular, from where it originates; and a second dimension, the horizontal spread, must not exceed 7 mm. Vascular involvement, either venous or lymphatic, should not alter the staging. The committee suggested that the diagnosis should be made on microscopic examination of removed tissue, preferably obtained by conization of the cervix, which should include the entire lesion. The criteria for the newly defined stage IA_2 therefore clearly exceed the criteria for microinvasion as defined by the SGO.

Current practice emphasizes the use of colposcopy in the diagnosis of preinvasive and invasive carcinomas. Conization of the cervix is reserved for distinguishing between microinvasion and true invasive carcinoma or those cases with positive endocervical curettage, discrepancy between cytology and biopsy, or unsatisfactory colposcopy results. In certain cases it may serve as a therapeutic modality. We have two major reservations concerning the new definition estalished by the FIGO. One is that it may be a difficult diagnosis to establish even with conization of the cervix. Our second concern is that since the stage IA_2 clearly exceeds the generally accepted definition as established by the SGO, there must be two separate treatment regimens for patients

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with a diagnosis of stage IA_2 cervical carcinoma. Traditionally stage IA carcinoma of the cervix has implied conservative surgery, such as cone biopsy or simple extrafascial hysterectomy. Therapy decisions regarding stage IA_2 without a clear understanding of the fine points of the definition may result in undertreatment of patients because the scope of the definition clearly exceeds the currently accepted criteria for conservative surgery.

This study was conducted to evaluate the ability to establish the histologic diagnosis of stage IA_2 by conization of the cervix and to evaluate the natural history and results of a group of patients with early invasive squamous cell carcinoma of the cervix with maximal treatment.

Material and methods

From 1976 through 1983 the Division of Gynecologic Oncology at the University of Washington Medical Center treated 50 patients with early invasive squamous cell carcinoma of the cervix in which a radical hysterectomy and pelvic lymph node dissection had been preceded by conization biopsy of the cervix. The clincial record and pathologic reports were reviewed on each patient. The patient's age, race, parity, initial cytologic results, presence or absence of gross lesions, whether the patient had colposcopy, and if so the outcome and adequacy of the examination, and the diagnosis on directed biopsies were recorded. The pathologic condition of the cone biopsy specimens was evaluated for positive or negative margins, depth of invasion, capillary-like space invasion, multifocal disease, and confluence. The horizontal spread of the tumors was not measured. The pathologic condition of each radical hysterectomy specimen was examined for residual disease after conization, extension beyond the cervix, and site and number of metastatic lymph nodes. A period of at least 5 years has elapsed since the treatment of each patient. The disease status, site of recurrence, subsequent treatments, and outcomes were recorded.

Results

The mean age of the 50 patients was 37 years (range, 22 to 72 years). The mean parity was 2.8. Forty-two of the patients were white and two each of native American, Oriental, black, and Mexican-American background.

Routine periodic screening was responsible for alerting the physician to the diagnosis in all but one instance. This patient had postmenopausal bleeding and an endocervical curettage demonstrated carcinoma in situ. In review, six other patients had a history of vaginal spotting. Forty-nine of the patients had cytologic studies performed at the initial examination. The Papanicolaou smears suggested carcinoma in situ in 22 patients and invasive cancer in 16. The cytologic condition was reported as merely "atypical" in 10 patients, 20% of the total group. One patient had a negative smear but a gross lesion. No visible lesion was present in 94% (47/50) of the patients. In the three patients with gross lesions, two had cone biopsy and the remaining patient had colposcopy and a biopsy consistent with carcinoma in situ but with questionable invasion.

Colposcopy was performed in 70% (35/50) of the women. Twenty-three of the examinations were considered adequate. The indications to proceed with conization of the cervix were based on a question of invasion in 15 patients, carcinoma in situ in six patients, and cervical intraepithelial neoplasia with a positive endocervical curettage in two patients. Twelve of the 35 patients undergoing colposcopy were considered to have inadequate examinations. Eight of those 12 patients had a biopsy diagnosis of carcinoma in situ. Four of the patients did not have biopsies and had conization of the cervix. Conization of the cervix without colposcopy was performed in 30% (15/50) of patients.

The cone biopsies were all performed by referring physicians, and the pathologic reports were reviewed at the University of Washington Medical Center. Positive margins for neoplasia on the cone were present in 66% (33/50) with invasive disease. Twenty-seven of those patients had residual carcinoma at the time of radical hysterectomy and pelvic lymph node dissection. Six of those 27 patients had only residual carcinoma in situ. There were six patients with positive margins at the time of conization of the cervix that revealed no evidence of residual disease at time of radical operation.

Negative margins on the conization specimen were confirmed in 17 of the 50 cases (34%). This represents a group of patients who would qualify as stage IA_2 carcinoma. Four of the 17 (24%) had residual invasive disease at the time of radical hysterectomy despite the negative margins on the cone biopsy specimen. Two additional patients had residual carcinoma in situ.

Capillary-like space invasion was demonstrated in 32% (16/50) of the conization specimens, multifocal invasion in 12% (6/50), and confluence was evident in 48% (24/50). Of the three patients with recurrent invasive carcinoma, one had all three other factors present, one had only confluence, and one was without any factors. No conclusion can be drawn from these findings.

Two patients had evidence of positive metastatic disease in the lymph nodes. One patient with a positive right common iliac node had a 2.2 mm invasive lesion with confluence on cone biopsy with negative margins and no residual cancer at the time of radical hysterectomy. The patient was treated postoperatively with radiation therapy of 5000 cGy to the whole pelvis and

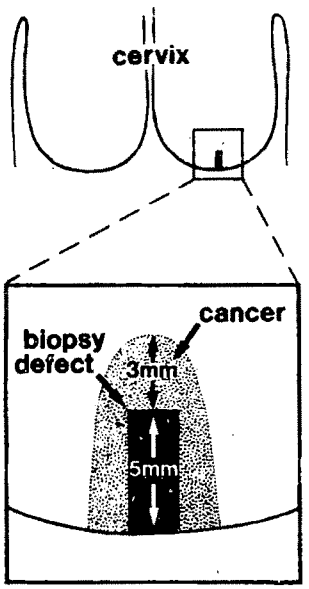


Fig. 1. This figure demonstrates the alteration in the depth of invasion after a cervical biopsy.

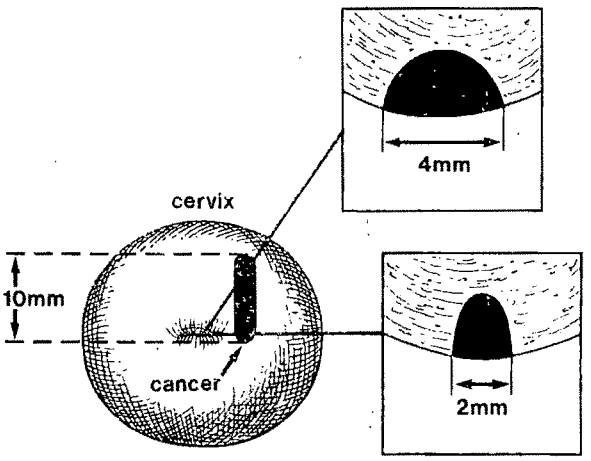


Fig. 2. The maximal horizontal spread of this cancer would not be demonstrated as a result of the radial histologic sections.

4500 cGy to the paraaortic lymph nodes to an upper border of T12. She is alive and free of disease at 87 months. The other patient is dead of disease despite postoperative radiation therapy.

Ninety-two percent (46/50) of the patients had follow-up. Forty-three of these 46 patients were followed up for more than 5 years. The range was from 8 to 123 months (mean follow-up, 68.3 months). There were four patients lost to follow-up in the immediate postoperative period when the patients returned to their referring community.

Four recurrences developed after treatment. One patient had carcinoma in situ at the apex and was treated successfully with an upper vaginectomy. Three patients recurred with invasive disease. One patient had recurrence both in the pelvis and liver at 25 months. The patient underwent palliative radiation therapy and chemotherapy and survived an additional 7 months. One of the patients had a positive left external iliac node and received 5000 cGy to the whole pelvis postoperatively and disease recurred 3 months later. She survived 3 months with additional treatment. One patient had recurrence of disease in the pelvis at 61 months after radical surgery. The patient underwent radiation therapy for the recurrence with whole pelvic external radiation and intraoperative electron beam therapy. Currently she is alive with disease.

Postoperative radiation therapy was administered to four patients. Two patients had positive lymph nodes; one of these patients is clinically without evidence of disease and one is dead of disease. Two patients had extension beyond the cervix on final pathologic review and received adjuvant whole pelvis radiation therapy. Both are clinically without evidence of disease. Two additional patients received radiation therapy for recurrent disease.

Comment

The new FIGO definition of stage IA_2 disease presumably evolved from the volumetric concepts of microinvasive disease.[3] These volumetric concepts have merit in a reserach setting but are impractical for clinical practice. The planar definition of the 5 mm depth of invasion and 7 mm of horizontal spread as adapted by FIGO was made without data to support its utilization.

A presumptive diagnosis of stage IA_2 carcinoma by cone biopsy of the cervix was possible in only 34% (17/50) of cases with early invasive carcinoma in this series of patients. Twenty-four percent (4/17) of these cases had residual cancer in the surgical specimen at the time of radial hysterectomy despite apparently negative margins at the time of the cone biopsy. One patient with 2.2 mm of invasion with negative margins had a positive common iliac node. The diagnosis of stage IA_2 disease becomes untenable if the lesion extends to or beyond the limits of the cone biopsy. This occurred in two thirds (33/50) of the cases of early carcinoma in this study. In such instances, it is customary to proceed with radical surgery because of the unknown depth of residual carcinoma. Although the diagnosis in each instance was established by cone biopsy, only 26% (13/50) of the cases of early carcinoma in this series could be appropriately considered as stage IA_2 lesions. The validity of such a staging classification must be open to challenge.

We can perceive two other major pitfalls in reaching the diagnosis of stage IA_2 carcinoma. Colposcopy and directed biopsy are integral steps in establishing the diagnosis of invasive cancer, and failure of the clinician to avail himself or herself of this approach would be widely criticized. Colposcopic biopsies were performed in 64% of the patients in this series. In each instance, the biopsy presumably removed part of the lesion and therefore may have altered the depth of invasion as seen on the final cone biopsy. This is illustrated in Fig. 1. The validity of a diagnosis of stage IA_2 carcinoma in any case when directed biopsies had encroached on the lesion in question could be justifiably rejected.

A second criticism involves the accepted techniques of pathologic study. Cone biopsy specimens, after initial fixation in formalin, are divided into quadrants and step-sectioned. The maximal extent of horizontal spread could be underestimated by this procedure. Fig. 2 demonstrates a narrow, long circumferential lesion in which the maximal horizontal spread would not be reflected by the histologic condition of the cone. The increasing use of laser conization of the cervix, with its attendant coagulation artifact that may obscure margins and depth of invasion, can only add to the difficulty of making a diagnosis.

The 4% incidence of metastatic lymph nodes and the 6% recurrence rate of invasive carcinoma in this series of cases with early invasive cancer emphasize the necessity of establishing guidelines for therapy. Unfortunately, there are too few patients in this series who "fit" the criteria for either the FIGO or SGO definition of microinvasion to make any conclusions or statements. Recent articles support the SGO definition for microinvasion.[4-7] Rarely patients with metastatic lesions have been reported with <3 mm of invasive cancer.[8] This was demonstrated in this series. Recently, the argument was advanced that guidelines advanced by the SGO may result in unnecessary radical surgery.[9] A more logical perspective is to consider the potential number of failures in the patients that exceed the SGO definition of microinvasion and still meet the criteria for stage IA_2 by the new FIGO definition. A recent paper summarizing reports in the literature concluded that the risk of metastatic disease in the lymph nodes in cases with <3 mm invasion does not exceed 1%.[5] Lesions with a depth of invasion between 3.1 and 5 mm have a nodal metastasis rate of 8%. The difference is highly statistically significant ($p < 0.001$). It would be unconscionable to accept this potential failure rate merely to reduce the number of radical hysterectomies performed for this disease. The literature does not provide clear direction concerning the issues of patterns of invasion, capillary-like space invasion, or horizontal spread.

A clear understanding of the problems in making a diagnosis and the implications of the histologic findings will permit experienced clinicians to make appropriate choices of treatment for their patients. Clinical staging has two purposes: it describes firm criteria that permit comparison of data and it establishes guidelines for treatment. The FIGO classification for stage IA_2 lesions would appear to adequately serve neither purpose. By contrast, the SGO definition for microinvasion serves a practical purpose, and conservative treatment in cases so defined will result in a cure in virtually all instances. Radical hysterectomy and pelvic lymph node dissection should be mandated for patients whose histologic findings exceed the SGO definition for microinvasion. This approach provides the maximum opportunity for cure of invasive cancer. At the next FIGO meeting the current definition of stage IA_2 should be reevaluated and modified to meet the requirements of clinical practice.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Conley G. Lacey, La Jolla, California. The authors retrospectively studied 50 patients with early squamous cell carcinoma of the cervix to determine the clinical feasibility of the FIGO cervical cancer classification system as it applies to stage IA_2 disease. All information was extracted from the patients' records. A measurement of the lesion diameter or breadth, a critical dimension of the FIGO system, was not included in the analysis.

Considerable useful information alerting us to the perils involved in the diagnosis and management of

early cervical cancer was obtained from this study. For example, the impracticality of the FIGO system is suggested by the fact that 33 of the 50 patients (66%) were excluded from FIGO substage IA_2 by virtue of positive cone margins. This is not as serious an indictment as it may sound, however, since as a practical matter, most patients with positive margins would be excluded from conservative treatment even with use of the SGO criteria, particularly if the margin was involved by invasive disease.

The remaining 17 patients in the study had negative cone margins and otherwise conformed to the author's criteria for FIGO stage IA_2. It is these 17 patients who should form the nucleus for this study and the analysis of these 17 patients must provide the evidence to refute the FIGO system. Six of these 17 patients had residual disease on the hysterectomy specimen, two with carcinoma in situ and four with microinvasive or invasive carcinoma. We do not know the outcome of these patients. It would also be helpful to know the exact millimeter-by-millimeter depth of invasion, the breadth of invasion, the presence of node or other metastases, the presence of other risk factors such as vascular space involvement, the recurrence rate, and the survival for this group of 17 patients. Whereas some of this information may be present in this study, it is not segregated from the 33 patients excluded on the basis of positive cone margins and therefore cannot be identified and used to refute the FIGO criteria for stage IA_2.

However, the authors do appropriately point out that the danger in use of FIGO stage IA_2 criteria for patient management is clearly documented in the literature, in which the reported incidence of pelvic lymph node metastases in patients with invasion between 3 and 5 mm is 8%. Dr. Greer, how many of the patients in this study had between 3 and 5 mm of invasion and what was the outcome of these patients?

This article is a modest impeachment of FIGO substage IA_2. It would be greatly strengthened by a careful pathologic review with inclusion of all FIGO criteria and other known risk factors. Results should be segregated according to those that do or do not conform to the study parameters. Thus, while I sympathize with the authors' opposition to FIGO substage IA_2, I cannot bring myself to join their indictment on the basis of the evidence presented in this paper.

I have one additional question. What were the characteristics of the four patients whose disease characteristics conformed to the FIGO criteria, who had negative cone margins but had residual invasive disease in the hysterectomy specimen?

Dr. Phillip Disaia, Irvine, California. I wish to defend the "Fathers of FIGO" at least in part. Until the new staging, we had a system that separated everything into microinvasion or stage IB. Stage IB encompassed everything from early stromal invasion to a 6 cm tumor. FIGO, in an attempt to define what Europeans term "microcarcinoma," studied the natural history of small cancers of the cervix. What is disappointing about this new staging system is that we do not have something to pass on to the practicing clinician. The FIGO staging system should not dictate therapy, and if we allow it to, we are misinformed. My recommendation is that clinicians apply the guidelines of the SGO, which were designed to help the clinican determine therapy. It has been the experience of most gynecologic oncologists that it is safe to apply the SGO guideline that simple hysterectomy is adequate for patients with <3 mm of invasion, with no vascular involvement, and no areas of confluence.

Dr. Greer, would you comment on that part of the SGO definition of microinvasion that has been controversial: confluence? Should it be included in the criteria? Finally, what is your recommendation to the practicing clinician about simple hysterectomy for patients with these lesions?

Dr. Frank R. Gamberdella, Santa Barbara, California. I was interested in the 17 cases with negative margins. I think you said four did not have negative results. You commented on the possible inadequacy of the carbon dioxide laser for conization. Should the clinician concerned about the possiblity of invasive lesion use a carbon dioxide laser cone or a traditional cold-knife cone for definitive diagnosis and better evaluation of the margins?

Dr. Greer (Closing). Dr. Disaia's question is the essence of this paper. As a gynecologic oncologist, I understand the implications of the FIGO classification. I have concerns about the interpretation of the FIGO classification in areas where tumor boards do not understand the implications of the definition of stage IA_2. They could recommend conservative management for a patient who needs radical surgery. As I pointed out in my conclusions, the experienced clinician will not fall into this trap. The SGO definition suitably fits the definition of microinvasion and the patient who fulfills these criteria can be conservatively managed. As presented in the text of the paper, no conclusions can be made regarding the risk factors of capillary-like space invasion, multifocal invasion, or confluence.

Twelve of the 17 patients with negative margins had invasions of ≤3 mm, and five patients had invasion of 3.1 to 5 mm. Residual invasive carcinoma at the time of radical operation was found in two patients in each measurement group. The four patients with residual invasive carcinoma are alive and free of disease after maximal treatment with radical operation. A patient with 1.8 mm of invasive carcinoma with capillary-like space invasion, confluence, multifocal invasion, and negative margins at the time of conization had recurrence at 61 months. She is alive with disease despite additional treatment.

Laser conization of the cervix with its coagulation artifact may obscure margins and depth of invasion. Any patient requiring a conization with a suggestion of invasion on the Papanicolaou smear, colposcopy, or biopsy should have cold-knife conization. This provides the most accurate information to make appropriate treatment decisions.

I have one additional comment. A recent article suggested that lesions invading between 3 and 5 mm could be adequately treated with a total abdominal hyster-

ectomy and a pelvic lymphadenectomy.[1] A 22.5% incidence of metastatic disease in parametrial lymph nodes in radical hysterectomy specimens has been recently reported.[2] Patients with stage IB invasive carcinoma of the cervix had an 11.4% incidence of positive parametrial nodes. These data are important to remember as we continue to evolve our guidelines for management of early invasive carcinoma of the cervix.

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Shirodkar cerclage in a multifactorial approach to the patient with advanced cervical changes

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Patients with a markedly effaced or dilated cervix and protruding membranes between 21 and 26 weeks' gestation were managed by Shirodkar cervical cerclage, perioperative tocolysis, broad-spectrum antibiotic therapy, and, in selected cases, inhibition of prostaglandin synthesis with indomethacin. The average duration of pregnancy after cerclage in nine patients was 11.8 weeks (range, 1 to 18 weeks). The mean birth weight was 2456 gm (range, 810 to 4341 gm). Eight of the nine pregnancies resulted in live infants (fetal survival rate, 89%); six patients (66%) were delivered at or near term. Preterm delivery occurred at 28 and 35 weeks' gestation in two patients and premature rupture of the membranes occurred in another at 25 weeks, 5 days after cerclage. There was no maternal postoperative or postpartum morbidity. A multifactorial approach to the patient with advanced cervical changes and protruding membranes in the second trimester resulted in a high rate of fetal survival and prolongation of pregnancy until term in the majority of patients. The Shirodkar cerclage holds a distensible cervix closed while the adjunctive medical therapy restores homeostasis. (AM J OBSTET GYNECOL 1990;162:1412-20.)

Key words: Shirodkar cerclage, indomethacin, tocolysis, antibiotics, preterm delivery

Most physicians manage cervical insufficiency with prophylactic cerclage placement with a modification of the technique described by Shirodkar[1] or McDonald.[2] Occasionally a woman is seen with a markedly effaced or dilated cervix, visible or protruding membranes, and a live intrauterine pregnancy. Results of cerclage placement in such unfavorable circumstances are acknowledged to be far less successful than when applied prophylactically. However, several authors have reported fetal salvage rates ranging from 47% to 91%.[2-5] It is commonly suggested that the McDonald cerclage (or modifications thereof) is the procedure of choice in the emergency situation, whereas some authors believe the Shirodkar procedure is technically not feasible for advanced cervical changes.[4, 6]

In this article we describe our experience with the Shirodkar cerclage in nine patients who were seen with a markedly effaced or dilated cervix and visible or protruding membranes. Management of these patients was augmented by preoperative and postoperative tocolysis, antibiotic therapy, and in selected cases, inhibition of prostaglandin synthesis.

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6/6/19903

Patients and methods

Nine consecutive patients from the authors' personal series in the 5-year period from 1984 to 1989 were treated by Shirodkar cerclage for advanced cervical effacement, dilatation, or both during the second trimester of pregnancy. Patients varied in age from 18 to 39 years. Six were multigravid and three were primigravid women. All patients were referred with the diagnosis of markedly effaced or dilated cervix with protruding or bulging membranes and presented between 21 and 26 weeks' gestation (mean gestational age at time of cerclage was 23.5 weeks). Three women presented with premature onset of contractions; five women presented with painless or silent cervical changes, and one presented with a displaced McDonald cerclage. The chief complaint that brought attention to the preterm cervical changes was a sensation of pelvic or vaginal pressure or a pink watery discharge in three patients. Symptomatic onset of uterine contractions was noted in three. Advanced cervical changes were detected in three patients on routine pelvic examination. Three patients had a positive history for diethylstilbestrol exposure in utero. Four of the nine patients had a history of second-trimester pregnancy loss or preterm delivery (Table I). Only one patient had a prior diagnosis of incompetent cervix; she had a previous McDonald cerclage placed at 14 weeks in the current pregnancy.

Selection criteria for inclusion in this series of patients were as follows: (1) cervical effacement greater than 60% and dilatation greater than 2 cm but less than 5 cm, (2) visible protrusion of intact fetal membranes beyond the internal cervical os or bulging at or beyond

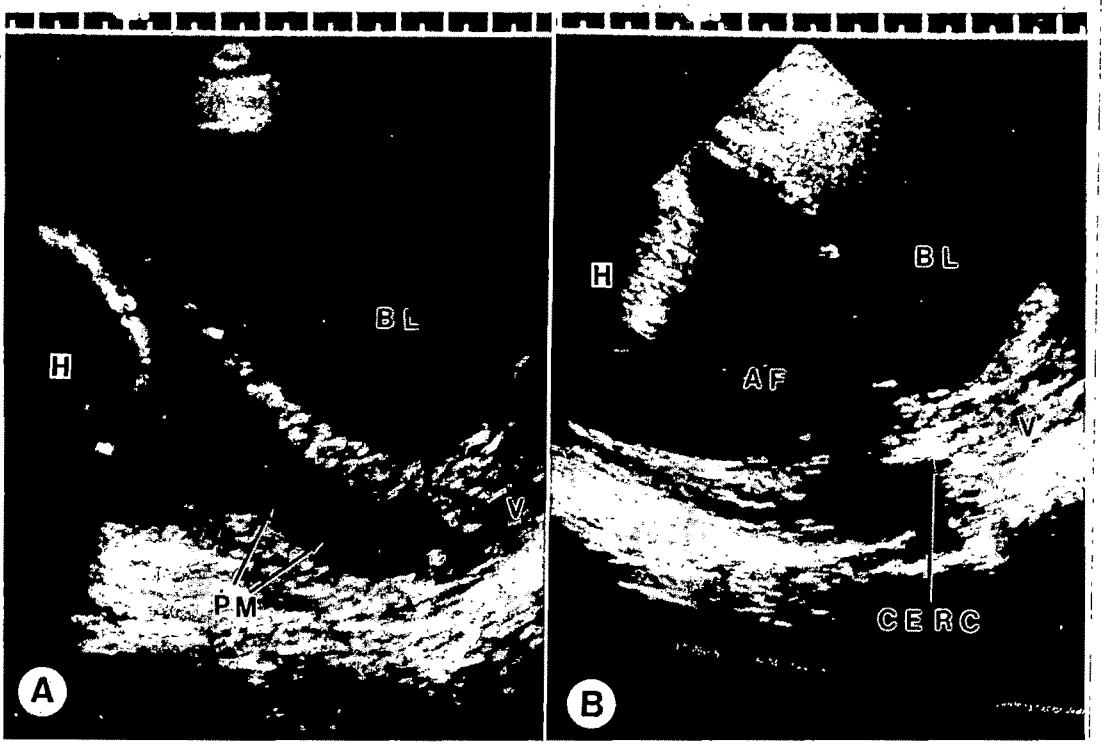


Fig. 1. Longitudinal scans of lower uterine segment and cervix (patient no. 4) by transabdominal ultrasonography before **(A)** and after **(B)** Shirodkar cerclage. *H,* fetal head; *AF,* amniotic fluid; *BL,* bladder; *PM,* prolapsed membrane; *CERC,* cerclage; *V,* vagina.

the external os, (3) a live intrauterine pregnancy of more than 20 weeks' and less than 27 weeks' gestation with no evidence of fetal anomalies, (4) absence of clinical evidence of chorioamnionitis, (5) absence of vaginal bleeding, and (6) favorable preoperative response to tocolysis.

The diagnosis of advanced cervical change and protrusion of the membranes was made by speculum or digital examination and confirmed by transabdominal ultrasonography (Fig. 1). The patient evaluation included cervical and urine cultures for aerobic and facultative bacteria. Cultures for genital mycoplasma organisms were obtained in several patients but were not routinely performed. Three patients had amniotic fluid cultures. All patients were admitted for observation and for continuous heart rate monitoring and uterine activity monitoring by external tocodynamometry. Patients were placed in moderate Trendelenburg position and, if the uterus was irritable, they received tocolysis by intravenous magnesium sulfate, ritodrine, or terbutaline, 0.25 mg, given subcutaneously according to standard procedures. Within 4 to 24 hours after admission and if uterine activity was absent or had substantially subsided, patients were taken to the operating room after informed consent had been obtained.

Surgical procedures. Deep general anesthesia was established with halothane or conduction anesthesia by subarachnoid block. Patients were placed in steep Trendelenburg position. The vulva was prepared in the usual manner, but the vagina was not cleansed by the nursing staff. After the open cervix was exposed with retractors, the vaginal walls and fornices were carefully prepared or irrigated with povidone-iodine solution under direct vision by the surgeon. Before operation, patients received 0.25 mg of terbutaline subcutaneously to further promote uterine relaxation and recession of protruding membranes. By means of sterile technique and ultrasonic guidance, amniotic fluid was removed (200 to 800 ml) in two cases by syringe to aid in decompression of the bulging membranes as previously described.[7]

The edges of the cervix were grasped gently by Babcock forceps or, if too thin and friable, the vaginal wall was grasped in the anterior and posterior fornices. The Shirodkar cerclage technique with modifications was used for the emergency cerclage (Fig. 2). The vaginal mucosa was incised transversely with long Metzenbaum scissors at the anterior and posterior cervical-vaginal junctions for a distance of 2 cm. Curved Allis forceps were used to grasp the anterior and posterior edges of the cut vaginal mucosa to compress the lateral paracervical tissue as previously described by Rust and Botte.[8] This maneuver facilitates passage of a 5 mm Mersilene tape (Ethicon RS-21, Ethicon, Inc., Somer-

Table I. Clinical data of patients with advanced cervical effacement treated by emergency Shirodkar cerclage

Patient no.	*Age (yr)*	*Gravidity*	*Parity (TPAL)*	*History*	*Gestational age at operation (wk)*	*Cervical status**	*Duration of pregnancy (wk)*	*Antibiotic therapy*
1	22	3	0-1-1-0	Presented with painless dilatation; previous second-trimester loss and preterm birth	25	100%; 3 cm; membranes bulging	38	Cefoxitin
2	37	3	1-1-0-3	Presented with painless dilatation; preterm delivery of twins	22	80%; 2-3 cm; membranes visible	40	Cefoxitin, erythromycin
3	18	3	0-2-0-2	Presented with premature contractions; DES exposure, previous 2 preterm births	26.5	100%; 4 cm; membranes bulging	28	Cefoxitin
4	29	3	1-0-1-1	Presented with painless dilatation	25	80%; 3 cm; membranes protruding	42	Ampicillin, clindamycin
5	36	1	0-0-0-0	Presented with premature contractions; uterine fibroid; cervical culture positive for *Gardnerella vaginalis*	23	90%; 3-4 cm; membranes bulging	39	Cefoxitin, erythromycin, Flagyl
6	28	3	0-1-0-0	Presented with displaced McDonald cerclage; DES exposure and previous preterm birth	24	100%; 2-3 cm; membranes visible	36	Amoxicillin
7	25	1	0-0-0-0	Presented with premature contractions; amniotic fluid positive for *Bacteroides* species	24	100%; 4 cm; membranes bulging	25	Cefoxitin, erythromycin
8	32	3	1-0-1-1	Presented with painless dilatation and twin gestation	21	70%; 3-4 cm; membranes protruding	38	Cefoxitin, erythromycin
9	39	1	0-0-0-0	Presented with painless effacement; DES exposure	21	100%; os covered by pseudomembrane; membranes bulging	34.5	Cefoxitin, erythromycin

TPAL, Term births, preterm births, abortions, living infants; *DES,* diethylstilbestrol; *SVD,* spontaneous vaginal delivery; *PROM,* premature rupture of membranes.

*Refers to cervical effacement and dilatation.

ville, N.J.) with large needle and blunt tip. A finger was placed in the cervical canal to guide the needle and to avoid perforating the cervix or the membranes. In two patients (No. 5 and No. 9), a second cerclage tape was placed above the first tape for security and to create additional cervical length. The knot was tied anteriorly and a tail of tape was left to protrude from the mucosal incision to ease removal before vaginal delivery.

Intravenous antibiotics were administered in the operating room before the cerclage procedure. With the exception of two patients who received ampicillin and clindamycin and amoxicillin, respectively, the other patients received cefoxitin, 2 gm intravenously, and treatment was continued for 24 to 72 hours after operation. In addition, five patients received erythromycin, 1 gm orally daily, for a minimum of 10 days after operation. Patients received intravenous magnesium sulfate or ritodrine in standard doses or subcutaneous terbutaline, 0.25 mg, as necessary for postoperative tocolysis. In the latter part of the study, we added indomethacin (Indocin, Merck, Sharp & Dohme, West Point, Pa.) sustained-release capsules, 75 mg orally twice daily for 3 to 7 days, to the protocol. Patient No. 5 required long-term indomethacin therapy for a total of 23 days because of intermittent episodes of premature contractions. Patients were seen at weekly intervals for pelvic evaluation of cervical length and effacement supplemented by transabdominal ultrasonographic examinations at frequent intervals. Doppler echocardiography was used to monitor fetal ductus flow velocity

Tocolytic therapy	*Delivery*	*Neonate*
Magnesium sulfate, terbutaline	Repeat cesarean section	Male, 2581 gm, living and well
Magnesium sulfate, terbutaline	Repeat cesarean section	Male, 3206 gm, living and well
Magnesium sulfate, ritodrine, terbutaline	Preterm labor SVD	Male, 950 gm, living and well
Magnesium sulfate, terbutaline	SVD	Male, 4341 gm, living and well
Magnesium sulfate, terbutaline, indomethacin	Outlet forceps	Male, 3865 gm, living and well
Ritodrine, terbutaline, indomethacin	SVD	Male, 3016 gm, living and well
Magnesium sulfate, terbutaline, indomethacin	PROM SVD	Viable male, 810 gm, neonatal death
Magnesium sulfate, terbutaline, indomethacin	SVD	Female, 1650 gm; female, 2150 gm, well
Terbutaline, indomethacin	PROM SVD	Male, 1986 gm, living and well

in three patients who received indomethacin. In the absence of progressive uterine contractions, patients were allowed to ambulate at will although vigorous physical activity was restricted. Intercourse was not contraindicated after a reasonable postoperative interval. Cerclage sutures were removed at 37 to 38 weeks' gestation, or whenever labor became established or after premature rupture of membranes (PROM).

Results

The results of emergency Shirodkar cerclage for the treatment of advanced cervical effacement, dilatation, and protruding fetal membranes are shown in Table I. The open cervix was closed without intraoperative complications or rupture of the membranes in all nine women. Two of the women had double sutures placed. Eight of the nine pregnancies continued and resulted in live births of infants (including one set of twins) who are living and well (fetal survival rate, 89%). Six patients (66%) were delivered at or near term by vaginal delivery or after repeat cesarean section. The average duration of pregnancy after cerclage placement was 11.8 weeks (range, 1 to 18 weeks). The average birth weight was 2456 gm (range, 810 to 4341 gm).

After elective cerclage removal spontaneous labor developed at or near term in four patients and repeat cesarean section was performed at term in two patients with the cerclage left in place. Preterm labor that did not respond to tocolysis occurred at 28 weeks' gestation in one patient (No. 3) and resulted in cerclage removal and vaginal delivery of a preterm infant that survived. Preterm premature rupture of the membranes occurred in one patient at 25 weeks' gestation (No. 7) 5 days after cerclage placement. *Bacteroides* species and gram-negative bacilli were isolated from the amniotic fluid in this patient. The cerclage was removed at the patient's request and an 810 gm infant was delivered that died 8 days post partum as a result of extreme prematurity and respiratory distress syndrome. Only three of the 10 infants were admitted to the neonatal intensive care unit. There were no operative or anesthetic complications, although prolonged Valsalva maneuver occurred before extubation in one patient who received a general anesthetic. Intraoperative blood loss was uniformly less than 125 ml. Partial displacement of the cerclage suture occurred in one patient at 36 weeks' gestation. Our patients did not experience clinical chorioamnionitis or postoperative or postpartum sepsis. Urine cultures were negative and cervical cultures grew normal vaginal flora except from patient No. 5 who had *Gardnerella vaginalis* infection. Amniotic fluid cultures were negative except in patient No. 7 as noted above. Microbiologic studies of the placentas and fetal membranes were not performed.

Comment

The patient with advanced cervical effacement and dilatation of the cervix and with membranes at the level of the external os or bulging into the vagina presents a formidable therapeutic challenge. At 27 to 28 weeks' gestation or thereafter, such patients are usually managed expectantly with bed rest and tocolysis and more recently with antibiotic therapy.[9] Survival rates exceed 90% in most neonatal intensive care units with infants with birth weights greater than 1000 gm. Despite this, short-term morbidity and the expense of neonatal intensive care are high, up to 33 weeks' gestation. The survival rate of infants weighing 500 to 999 gm is only 30% to 40% and of these survivors, one fourth are moderately to severely handicapped.[10] Therefore every reasonable effort should be made to prolong gestation safety for the previable or very-low-birth-weight fetus.

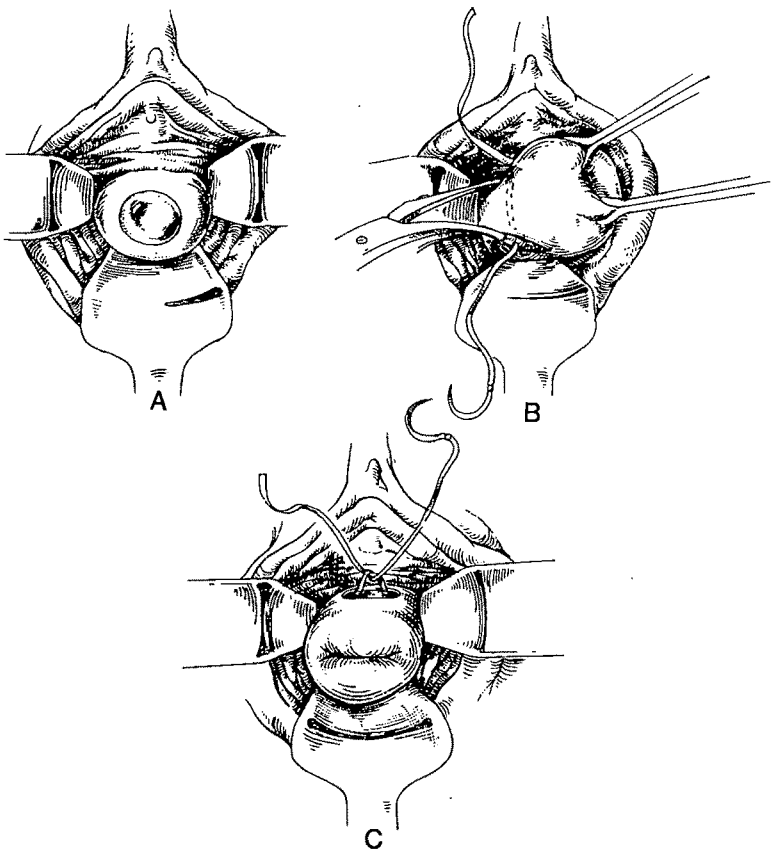


Fig. 2. Modified Shirodkar technique. **A,** Open cervix and protruding membranes are exposed with retractors. **B,** Cervical edges are grasped with Babcock forceps. Curved Allis forceps grasp edges of incised anterior and posterior vaginal mucosa and compress paracervical tissue, thereby facilitating passage of the needle with 5 mm Mersilene tape (Ethicon RS-21). **C,** After the membranes have been reduced, the cervix is closed by tying knot anteriorly.

The results of this uncontrolled series of patients suggest that emergency cerclage up to 26 weeks' gestation has an important role in promoting fetal survival. Our success rate in terms of infant survival was 89%, and six of nine patients were delivered at or near term without maternal complications. It is the experience of most obstetricians that unless the open and effaced cervix with bulging membranes is closed surgically in the second trimester, it is unlikely for such a patient to carry the pregnancy to viability and exceedingly rare to reach term.[4] Goodlin[5] reported that preterm delivery was inevitable and the fetal survival only 20% in patients treated expectantly for bulging membranes between 23 and 27 weeks' gestation. Similar results were reported by Varma et al.[11]

Although Shirodkar and McDonald techniques have been used by various authors with approximately equal frequency (Table II), there is a bias that the McDonald suture is technically easier, requires less operating time, produces less surgical trauma to the cervix, and is especially applicable to the emergency situation.[2, 6] Some authors have even stated that it is technically not advisable to close the cervix with a Shirodkar-type cerclage when the cervix is effaced.[4] Our experience is at odds with that view. We suggest the Shirodkar method has the following advantages for emergency as well as prophylactic cerclage: (1) stronger circumferential support because it is placed closer to the cervical and uterine-isthmic junction, (2) less chance of suture displacement or erosion through the cervix, and (3) protection of membranes from accidental puncture or trauma (abrasion) because of paracervical rather than intracervical placement of the suture.

The key elements to successful placement of a Shirodkar cerclage under emergency conditions are as follows: (1) uterine relaxation by preoperative and intraoperative administration of terbulatine, (2) decompression of bulging membranes by steep Trendelenburg position, ultrasonically guided amniocentesis if necessary, or other maneuver such as bladder distention,[12] (3) traction at the cervical-vaginal junction if the cervix is markedly effaced, and (4) use of a curved Allis forceps to compress the paracervical tissue at 3-o'clock and 9-o'clock positions to facilitate passage of the suture

Table II. Cumulative results of therapeutic cerclage during the second trimester of pregnancy

Author	*Method*	*No. of patients*	*Fetal survival rate (%)*
Lauersen and Fuchs[3] (1973)	Shirodkar cerclage; postoperative alcohol	57	79
McDonald[2] (1980)	Purse-string cerclage	76	47
Harger[13] (1980)	McDonald purse-string or Shirodkar cerclage	49	59
Charles and Edwards[14] (1981)	Shirodkar cerclage	46	61
Olatunbosun and Dyck[4] (1981)*	Double purse-string plus modified Wurm suture; antibiotics	12	83
Goodlin[5] (1987)*	McDonald purse-string plus Wurm sutures; antibiotics and terbutaline	11	91
Novy et al. (this series, 1989)*	Shirodkar cerclage; antibiotics, terbutaline, and indomethacin	9	89

*Advanced cervical effacement or dilatation with protruding or bulging membranes.

(Fig. 2, *B*). Although we have had equal success with general and conduction anesthesia, we prefer the latter to minimize the hazard of maternal straining during induction of anesthesia or during extubation.

The most frequently encountered complication of emergency cerclage in the presence of bulging membranes is rupture of the membranes during the perioperative period. Intraoperative rupture of the membranes was observed in 30% of the patients at Magee's Hospital[18] and in 17% of the patients reported by Olatunbosun and Dyck.[4] Goodlin[5] reported a combined 45% incidence of membrane rupture at operation or within 4 days after cerclage but his patients had unusually wide cervical dilatation (≥4 cm) and more than half had twins or triplets. We did not experience intraoperative rupture of the membranes in our nine patients but one patient who demonstrated positive amniotic fluid bacterial cultures did have rupture of the membranes 5 days after operation.

Uterine irritability and chorioamnionitis are other potential postoperative complications.[14] The majority of our patients demonstrated some degree of uterine irritability before cerclage (4 to 10 contractions per hour), although only three patients had symptomatic contractions. We have previously demonstrated a transient and modest increase in maternal plasma prostaglandin metabolites after cervical cerclage procedures.[15] Mean basal levels and the rise in prostaglandin metabolites were not related to cerclage type, trimester of pregnancy, or cervical status provided that dilatation was ≤3 cm, and effacement was ≤60%. Highest basal and postcerclage prostaglandin metabolite levels were associated with advanced cervical changes, uterine contractions, and membrane prolapse or rupture. Therefore we do not recommend routine administration of prostaglandin synthetase inhibitors for prophylactic cerclage procedures, even those performed in the second trimester. However, patients with advanced cervical changes in whom an emergency procedure is performed may benefit from use of antiprostaglandins.

It is likely that infectious complications after cerclage arise as a result of preexisting subclinical infection of the decidua or chorioamnion. This hypothesis is supported by the following data. (1) The recovery of microorganisms from the chorioamnion (in patients without cerclage) is strongly related to both histologic chorioamnionitis and to prematurity, yet most patients with histologic chorioamnionitis have no clinical signs of infection.[16] (2) Intrauterine infection increases prostaglandin production[17] and basal prostaglandin levels are increased in patients with advanced cervical changes and protruding membranes.[15] (3) The presence of cerclage at the time of premature rupture of the membranes does not increase maternal or neonatal infectious morbidity.[18]

Goodlin[5] maintained eight patients for 2 to 14 weeks after premature rupture of the membranes with cerclage in place without sepsis, although he did observe intrauterine growth retardation in several infants. There are increasing data to indicate that the risks associated with prematurity largely exceed the risks of infection.[18] In the absence of clinical chorioamnionitis, immediate removal of the cerclage after premature rupture of the membranes may not be advisable for the very premature fetus.

The strong association between infection within the uterus and prematurity suggests that microbial factors play an important role in a large percentage of previously unexplained preterm births. Cervical or vaginal microflora or the inflammatory reactions they produce release factors (e.g., proteases, collagenases, prostaglandins, and lymphokines) that initiate or predispose to uterine contractions, cervical ripening, and rupture of membranes.[17, 19] Microorganisms are recovered from the chorioamnion in the majority of women with preterm labor.[16] The recovery of bacteria within fetal membranes is fivefold higher than from amniotic fluid, suggesting that positive amniotic fluid cultures represent a later stage of ascending infection.[16, 20] Women in preterm labor with infected amniotic fluid tend to be delivered at earlier gestational ages despite tocolytic therapy than women with sterile fluid.[20] Although there are

Table III. Measurements of fetal ductus arteriosus blood flow velocity after indomethacin therapy

Patient no.	*Gestational age (wk)*	*Systolic velocity (cm/sec)*		*Diastolic velocity (cm/sec)*		*Tricuspid regurgitation*
		Baseline	*During therapy*	*Baseline*	*During therapy*	
5	23	100	120	10	20	No
	25		80		10	No
	26		140		8	No
	26.5	100		12		No
8						
Twin A	21	90	100	5-10	10	No
	22	90		8		No
Twin B	21	80	90	5-10	10	No
	22	80		10		No
7	24		120		8	No
	24		100		14	No

occasional reports of successful treatment of intraamniotic infection with antibiotic therapy,[21] it is likely that detection of microorganisms in amniotic fluid will identify patients who are less suitable candidates for emergency cerclage because such patients have a higher incidence of failure and postoperative complications.[5, 14]

We treated our patients empirically with broad-spectrum intravenous antibiotics (e.g., cefoxitin) at operation and for several days after operation because subclinical infection of the chorioamnion (with anaerobic and facultative organisms) was likely. The use of erythromycin for 10 to 20 days is supported by recent evidence that antibiotics (including erythromycin and clindamycin) inhibit microbial proteases and that erythromycin (1 gm per day) given as an adjunct to tocolysis of preterm labor was associated with prolongation of pregnancy.[9] A historical comparison from the literature indicates a higher success with cerclage when adjunctive antibiotics were used (Table II). Multicenter studies are currently in progress to determine the role antimicrobial agents will play in the management of preterm labor.

We used the prostaglandin synthetase inhibitor indomethacin as part of our multifactorial approach in five patients because inflammatory disruption of decidual and membrane lysosomes increases local concentrations of arachidonic acid and thereby stimulates prostaglandin production.[22] Moreover, a variety of genital tract microorganisms produce phospholipases that augment the local release of prostaglandins.[19] Prostaglandins stimulate myometrial activity and promote collagen breakdown and cervical ripening, whereas indomethacin is known to arrest premature labor.[22] Short-term indomethacin treatment has little or no adverse effect on fetal well-being or neonatal outcome but prolonged indomethacin treatment is associated with oligohydramnios.[22, 23]

There were no apparent complications in our patients who received indomethacin 150 mg daily for periods of 3 to 7 days. In a recent study an increase in ductal velocity (suggesting constriction) was observed in 50% of indomethacin-treated fetuses between 27 and 31 weeks' gestation.[24] In all cases ductal constriction resolved within 24 hours after the cessation of indomethacin therapy. We performed fetal Doppler echocardiography and flow velocimetry during indomethacin therapy in three of our patients—two with singleton pregnancies at 23 and 24 weeks' gestation and the other with a twin pregnancy at 21 weeks' gestation. The results are shown in Table III. Only a small increase in ductal flow velocity was observed in the fetus of patient no. 5 after 23 days of indomethacin, and treatment was then discontinued. There appears to be a higher margin of safety with indomethacin use in the second trimester of pregnancy because the ductus of the very premature fetus is less sensitive to prostaglandin inhibition.[22, 24]

In summary, our initial results in nine patients indicate that an aggressive multifactorial approach to advanced cervical dilatation and effacement before 27 weeks' gestation (combining cervical cerclage, antibiotics, tocolytic therapy, and inhibition of prostaglandin synthesis) is associated with a high rate of fetal survival and with prolongation of pregnancy until term in the majority of patients. Retrospective control groups indicate that patients who have advanced cervical changes with protruding membranes during the second trimester have low fetal survival rates and a poor chance of reaching term. Moreover, patients who have cerclage placement are able to resume reduced physical activity, whereas similar patients treated without operative intervention generally require complete bed rest. Although our multifactorial approach is based on well-defined pathophysiologic mechanisms, the relative importance of the component parts needs to be evaluated in controlled and randomized prospective trials.

From a mechanistic standpoint, we view cerclage as a means to protect the fetal membranes from direct exposure to bacterial products (e.g., proteases) in the lower genital tract, to slow the rate of ascending infec-

tion, and, most importantly, to provide support against further prolapse and herniation of the membranes. A successful cerclage does not prevent the ripening process but it holds a distensible cervix closed while the adjunctive medical therapy is directed to remove the inciting stimuli and to restore homeostasis.

We thank Drs. Miles Seeley, Desmond Johnson, John Buckmaster, and Russell Dow for the opportunity to treat their patients. We acknowledge the expert assistance of Dr. Mary Jo Rice and Dr. Amy Thurmond in performing fetal echocardiography and cervical ultrasonography, respectively.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Robert C. Goodlin, Denver, Colorado. In obstetrics, success is all that counts. If the diagnosis and procedures are all incorrect, but there is a good outcome, that is far better for the patient and the obstetrician than the reverse. Dr. Novy and colleagues have had a wonderful outcome for nine difficult cases, and have described some original concepts.

The modification and use of the Shirodkar technique in emergent situations is a major contribution. In the case with wide cervical dilation, I use both the Wurm and the McDonald cerclage. An intracervical inflated Foley bag keeps the membranes out of sight. Several of my colleagues use the Shirodkar technique. My sutures and knots are more likely to stay tight than theirs.

Dr. Novy speaks of ultrasonographic examination of the cervix. In the patient with a previable fetus and bulging membranes, I hope that a perineal ultrasonographic examination will be done of her cervix before rupturing the membranes or asking the patient to push. Often the membranes are in an hourglass pattern through a partially dilated cervix.

In my experience intraamniotic injection of high-dose antibiotics would have effectively treated Dr. Novy's case of chorioamnionitis and saved the pregnancy. Others consider this to too risky. Conversely, Dr. Novy places a cerclage in patients treated for premature labor with tocolytic agents, which seems a bit risky to me. The most risky procedure of all must be to place a cerclage in patients with a twin pregnancy after delivery of a nonviable twin. These risky procedures occur throughout the country, and I wonder what sort of informed consent Dr. Novy obtains for his technique.

Our colleagues are now demanding properly performed clinical trials, despite the fact that most of the progress in our field has come from case reports like Dr. Novy's. As an article of faith, I believe that a cerclage before the twenty-sixth week should be considered whenever there is significant cervical dilatation in the absence of painful contractions. However, our house

officers recently declined my advice and put to bed in our hospital a woman at 24 weeks' gestation with a cervix dilated 3 to 4 cm and with bulging membranes; she remained at bed rest for 10 weeks. Labor was induced at 37 weeks because of a fetus with intrauterine growth retardation. The costs of a randomized trial of bed rest versus cerclage, if done properly, would be tremendous. If our colleagues demand this before using the technique in advanced cases of cervical dilatation with previable fetuses, their patients will suffer preventable losses. Although Dr. Novy speaks of a clinical trial, I wonder if he would be willing to participate, given his own success?

One of the correlations I have noted with patients with advance cervical changes, is a subsequent fetus with intrauterine growth retardation. This is apparently true in Dr. Novy's experience and probably represents the spectrum of premature labor. My final question, Dr. Novy, is when does a case of incompetent cervix become premature labor?

Dr. Raphael B. Durfee, San Diego, California. Dr. Novy continued where many of us left off. To those, like me, who were pioneers in the use of cerclage it is very complimentary to have him adapt this old procedure to modern situations. I did the third and fourth cerclages in the United States, in the Army Hospital in Fort Leavenworth, Kansas. I used kangaroo gut that came in a test tube and the operation was successful. Dr. Novy also helped to further a procedure that Dr. Ralph Benson and I introduced called abdominal cerclage. One problem that we have always had is the management of prolapsed membranes. Dr. Louis Gluck, a perinatologist with us at University of California, San Diego for many years, was of the opinion that all these women had some degree of infection of the amnion. He thought that cervical incompetence was not an anatomic failure necessarily, but often a functional one related to various aspects of infection. Dr. Novy has made an incredibly important contribution to the use of this procedure by using differrent antibiotics to manage potential, if not actual, infection. His sucess rate reflects this. Dr. Novy, how do you avoid tying part of the prolapsed membranes into the cervical canal tissue when you tie down the cerclage tape? If you produced enough pressure to cause necrosis, you would defeat your purpose.

Dr. Russell K. Laros, San Francisco, California. One trick we have used to deal with the problem of avoiding the membranes has been to use a Foley catheter with a 60 ml balloon. The catheter tip is cut off and the balloon is filled with water. The balloon is used to push the membranes inside as you tie down the cerclage and then the balloon is deflated. The method has been very helpful and eliminates the problem of catching the membranes in the suture.

Dr. Novy (Closing). I have been concerned about the use of the Wurm and McDonald sutures for emergency cerclage because they do not hold well in a markedly effaced and thinned cervix. There is an increased hazard of perforating the membranes each time the needle is passed through the substance of the cervix. It has always seemed more rational to use an encircling band of the Shirodkar type to take advantage of the paracervical tissue as much as possible. Naturally, successful application of the cerclage requires at least partial reduction of the herniated membranes. Transabdominal aspiration of amniotic fluid will not be successful in helping to reduce the membranes unless the uterus is sufficiently relaxed. On several occasions, I have applied a second cerclage higher up while exerting traction on the first suture. A curved Allis forceps is useful to compress the paracervical tissue and displace the membrane so that the risk of puncture is minimized.

We do obtain informed consent from our patients and emphasize the risks of intraoperative and postoperative rupture of membranes. We have been happy with our low or absent maternal morbidity. If we include patients who have positive amniotic fluid cultures, we may expect to see more complications. We are designing a prospective trial at our institution and, in my opinion, part of the protocol should include identification of infections in the amniotic fluid. This represents a later stage of ascending infection, which is associated with a higher incidence of complications such as premature rupture of the membranes and chorioamnionitis. Intrauterine growth retardation may be associated with various conditions for which cerclage is performed, such as bicornuate or unicornuate uterus, but it is not a complication of cerclage per se provided there is normal amniotic fluid volume.

When does an incompetent cervix become premature labor? Dr. Durfee suggested an answer in his comment. In a substantial percentage of patients preterm labor will present painlessly as a functionally "incompetent cervix" but uterine irritability will be detected by careful monitoring. Prostaglandin release by microorganisms or inflammatory cell products leads to the triad of cervical softening, uterine contractions, and weakening or rupture of the membranes. Depending on host factors, any one part of this triad may be prominent clinically in one patient and not in another. This would explain why primigravid patients who lack an anatomically defective cervix develop "painless cervical dilatation" and why the incompetent cervical os syndrome is not always repetitive. For these reasons, we should include functional causes in our differential diagnosis of preterm labor and cervical incompetence. This, in turn, leads logically to an integrated, multifactorial approach to therapy.

What is fetal distress?

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Fetal distress is a widely used but poorly defined term. This confusion of definition compounds the difficulty of making an accurate diagnosis and initiating appropriate treatment. The fetus reacts at the onset of asphyxia with a remarkable series of responses, primarily a complexly regulated redistribution of blood flow that serves to limit the deleterious effects of oxygen limitation in vital organs. This enables the fetus to survive asphyxia intact unless the insult is profound or prolonged. The most common asphyxial stresses imposed on the fetus during labor are insufficiency of uterine blood flow, or insufficiency of umbilical blood flow, and occasionally decrease in uterine arterial oxygenation. Each of these stresses produces characteristic fetal heart rate patterns: late decelerations, variable decelerations, or prolonged bradycardia. There is strong evidence that the presence of normal fetal heart rate variability represents normal central nervous system integrity, including adequate oxygenation. A decrease or loss of variability in the presence of these patterns is a sign that the physiologic compensations are overwhelmed as a result of the severity of asphyxia. Knowledge of the fetal responses to asphyxia, together with the known evolution of fetal heart rate patterns during asphyxia, should allow a more accurate definition of the onset of unacceptable asphyxia, and more rational management and timing of intervention. (AM J OBSTET GYNECOL 1990;162: 1421-7.)

Key words: Asphyxia, fetal distress, fetal heart rate monitoring, fetal physiology

The term *fetal distress* is widely used as an indication for cesarean section, or as justification for midforceps delivery. It is often prefaced by the term *acute* or *chronic*. Some authors have defined it as "late decelerations," "severe variable decelerations," or "tachycardia with total loss of short-term variability" of the fetal heart rate.[1, 2] Others believe that fetal acidosis is necessary to define fetal distress, or they imply that a depressed Apgar score is required.[3]

Most physicians recognize that fetal distress is related to asphyxia, with the implication that it should be avoided. We, and others,[4] believe that fetal distress is a poorly defined term, and that this diffuseness of understanding is a disservice to obstetrics. We believe that the term can be more accurately defined with our current understanding of fetal cardiorespiratory responses during labor, and that a better understanding of the pathophysiology of asphyxia will result in improved management of the fetus during labor.

Asphyxia and fetal morbidity

Asphyxia has the pathologic meaning of insufficiency or absence of exchange of the respiratory gases, although etymologically it is derived from the Greek word meaning pulseless. Its severity is described in terms of acidosis, hypoxemia, and hypercarbia. With prolonged hypoxia, anaerobic metabolism within the organism results in lactic acidemia, which aggravates the acidosis.

In a strict sense all fetuses are born "asphyxiated" because there is a mixed respiratory and metabolic acidosis and hypoxemia in newborns with a totally normal intrapartum course and outcome. In a series of 899 fetuses, at birth the mean umbilical arterial pH was 7.2 (SD ± 0.08) and base excess −8.3 mmol/L (SD ± 4.0).[3] The carbon dioxide tension calculated from these means is 49 mm Hg. This "asphyxia" is mild in nature and is not considered a pathologic condition. Such blood gas levels at birth may even be physiologic, to ensure the rapid assumption of the adult circulation and respiration. It is noteworthy that the range of normality calculated as mean − 1 SD is extreme, including a pH as low as 7.12, and base excess to −12 mmol/L.

Severe fetal asphyxia can cause cerebral palsy and lesser degrees of neurologic damage, although it is now clear that the proportion of cerebral palsy caused by birth asphyxia is relatively small, perhaps less than 10%.[5, 6] The degree of damage to any individual fetus after severe asphyxia can be quite variable. For example, some fetuses may not survive the episode in utero, others have central damage that results in a surviving newborn with neurologic defects, and still others survive without apparent deficits.[7-9]

At one end of the scale, we have reasonably good evidence for the limits of fetal tolerance for complete

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absence of oxygen delivery. Myers[10] showed that after complete cessation of fetal oxygen delivery, hypoxemia and both respiratory and metabolic acidosis occurred rapidly. Intact survival generally did not occur after 10 minutes of oxygen deprivation. Survivors generally had brain stem lesions, although the patterns of damage were variable. If oxygen delivery was prevented for 25 minutes, fetuses could be resuscitated but apparently the hypoxic damage to numerous organs including the heart was so severe that death occurred within a short time. Myers et al.[10-12] have also studied prolonged partial asphyxia in sheep and monkeys as a result of a variety of mechanisms. As with brief complete asphyxia, they found a variable pattern of response. Survivors generally had neurologic deficts as a result of cortical lesions, in contrast to those subjected to complete oxygen cessation. Prolonged partial asphyxia in the above studies has been difficult to define, probably because of the several components, such as degree of hypoxemia, duration, and initial condition of the fetus.

Although several other workers have attempted to relate fetal asphyxia to electrophysiologic or histologic effects on the brain,[13-16] the majority of studies of fetal asphyxia have concerned fetal physiologic responses, including cerebral oxygen uptake to brief periods of asphyxia without benefits of electrophysiologic, pathologic, or behavioral follow-up.[17-22] We believe that ideally it is better to quantitate severity of asphyxia by such measures as adequacy of cerebral or myocardial oxygenation. Currently there is no linkage of the pathophysiologic quantification of asphyxia with electrophysiologic consequences that signify unacceptable damage.

The production of cerebral damage under controlled physiologic conditions has proved to be difficult. It is known that asphyxia sufficient to result in a preductal arterial oxygen content below 1 mmol/L usually is associated with reduced cerebral blood flow and oxygen uptake.[23] However, such asphyxia does not necessarily result in irreversible electrocorticographic changes, or cause neuronal necrosis.[24] The fetus is apparently able to temporarily lower its cerebral metabolism by various compensatory mechanisms.[25] There are strong suggestions from the literature regarding newborns that hypotension is necessary for cerebral damage, but this is not unequivocally demonstrated for the fetus. It seems evident, however, that minor or brief periods of asphyxia per se do not cause cerebral damage. The insult must be profound and prolonged,[7-9] but the quantitative details have not yet been established.

If all infants are born with at least "physiologic" asphyxia, and in the extreme case severe asphyxia causes brain damage, how then can we recognize the transition zone? It is clearly important to recognize the transition because if obstetric intervention occurs too early, it may be inappropriate, or if too late, the fetus may be damaged. A tentative definition of fetal distress follows: persistent fetal asphyxia that, if not corrected or circumvented, will result in permanent neurologic damage or death.

This is not a particularly valuable working definition unless clinical markers of impending or actual fetal neurologic damage can be defined.

Fetal responses to asphyxia

There have been many recent studies of fetal responses to oxygen limitation provoked by various means, including reduced uterine and umbilical blood flows.[26] It is now well established that a number of important cardiorespiratory adjustments occur during hypoxia or asphyxia to preserve the oxygenation of certain "priority" organs. Initially there is a selective vasoconstriction of certain organs and vasodilatation of others, which results in an increased blood flow to the brain, heart, and adrenal gland, retention of blood flow to the placenta, and decreases in blood flow to the other organs or areas of the body.[27, 28] The overall cardiac output remains fairly stable at moderate degrees of hypoxia, but at more severe degrees of hypoxia or asphyxia cardiac output decreases.[29, 30]

A further compensatory response is that overall fetal oxygen consumption declines to values as low as 50% of control.[31] This level can be maintained for periods of up to 45 minutes and is completely reversible on cessation of hypoxia. It is thought that this represents a decrease in oxygen consumption in those vascular beds where circulation is inadequate. There is gradual development of a metabolic acidosis, primarily as a result of the accumulation of lactate.[32] This probably represents anaerobic glycolysis in those vascular beds where oxygen supply is limited.

Numerous mechanisms responsible for these hemodynamic alterations have been identified. These include oxygen levels,[17, 33] carbon dioxide tension,[34] α-adrenergic activity,[35] β-adrenergic activity,[36] arginine vasopressin,[37] endogenous opioids,[38] and prostaglandins.[39] There are undoubtedly other as yet unidentified mechanisms.

When asphyxia becomes severe, these protective mechanisms are overwhelmed, and there is intense vasoconstriction of all vascular beds.[29] At such degrees of hypoxia, blood flow to and, therefore, oxygen consumption of all organs, including those previously favored, most likely decreases. Cerebral and myocardial oxygen consumption can be maintained during moderate hypoxia by the increase in blood flow to the respective organ that exactly balances a decrease in arteriovenous oxygen content difference.[17, 40] However, at more severe degrees of asphyxia, when an adequate compensatory increase in blood flow to the organs no

longer occurs, the oxygen consumption can no longer be maintained.[22, 23] This represents a point of decompensation of the physiologic mechanisms that had previously lessened the impact of relatively short periods of asphyxia on fetal vital organs. This stage most likely precedes the final bradycardia, hypotension, and death by a relatively short time. It is thought that hypoxic organ damage occurs during this phase. However, such observations do not assist in recognition of the degree of oxygen consumption deficit that can be tolerated before permanent damage occurs. This will require a combination of metabolic, electrophysiologic and pathologic studies.

Prognostic capacity of FHR variability

It was commonly stated in the past that fetal heart rate monitoring is extremely accurate in diagnosing fetal vigor when the pattern is normal, but that it is poor for determining depression when the pattern is "abnormal."[41, 42] That is, its specificity, or ability to correctly diagnose normal, was thought to be poor. This resulted in the overdiagnosis of "fetal distress," and at times unnecessary intervention leading to either cesarean section or potentially traumatic operative vaginal deliveries. We believe that this may be true if fetal heart rate (FHR) patterns are interpreted according to older concepts that considered the prominent "abnormality" to be decelerations of FHR with contractions.

Empirical clinical evidence strongly suggests that the addition of the determination of FHR variability to the FHR pattern interpretation can aid in improving specificity. Evidence for this view has taken the form of clinical observations[43] or retrospective surveys of outcome after monitoring.[44-46] The common trend in these studies is that the presence of FHR variability is almost invariably associated with fetal vigor at birth, even in the presence of various decelerations or bradycardias. A further observation is that of infants who died in utero while being monitored, none had the presence of normal FHR variability.[47] The corollary of this observation is that if the FHR has normal variability, the fetus is at low risk for immediate death caused by asphyxia.

The preceding observations and widespread clinical experience have resulted in the acceptance of FHR variability by many clinicians as a prime indicator of fetal vigor.[47] The acceptance of the efficacy of this approach to FHR interpretation is not, however, universal,[48-50] and we believe that the overdiagnosis of the "asphyxiated" fetus will continue until a physiologic basis for FHR variability is demonstrated, leading to more rational interpretation. The original interpretation of FHR patterns stressed the decelerations (late or variable decelerations) occurring with contractions, and equated their presence to "fetal distress," which then dictated operative intervention.[51] The alternative interpretation states that the decelerations, or bradycardias, indicate intermittent asphyxial "stresses" (generally insufficiency of uterine or umbilical blood flow), whereas the collective influence of these stresses on the fetal physiologic compensatory mechanisms is determined by the decrease or loss of FHR variability, signifying a cumulative oxygen debt and decompensation.[47] Thus the presence of FHR variability indicates central (nervous system, myocardial, or both) normoxia, whereas its decrease in the presence of the stress patterns indicates a decrease in the oxygenation of these organs.

It has long been recognized that FHR variability can be affected by numerous influences other than asphyxia. Such influences include congenital anomalies and drugs, and in some cases there is no apparent cause, although the infant is normal at birth. Examples of some factors responsible for decreased or absent variability include anencephaly, complete heart block, narcotic administration (presumably acting on the central nervous system), and atropine administration (presumably blocking oscillatory influences transmitted by the vagus nerve).[26]

The source of FHR variability is clearly complex, with inputs from many cycling physiologic phenomena, including respiratory arrhythmia, blood pressure fluctuations, and thermoregulation, at least in the adult.[52] However, many of the observations are most consistent with the theory that the presence of normal variability requires integrity of (1) the cerebral cortex, (2) the midbrain, (3) the vagus nerve, and (4) the cardiac conduction system.[47]

It is known that different fetuses have an intrinsic "quantity" of variability, and also that this can change with differences in fetal state.[53-55] It is also known that the components used to describe fetal state can be altered by hypoxia or hypercapnia[56] and by short periods of decreased uterine blood flow.[57, 58] Again, the presence of certain state variables can affect others; for example, during fetal breathing movements there is a respiratory arrhythmia,[59] and during prelabor myometrial activity there is a change to the quiescent state in fetal sheep.[60] It is important to be aware of such activities to make the appropriate distinction between asphyxial and nonasphyxial causes of decreased variability.

Clinical implications

There are basically three common means by which the human fetus can become asphyxiated (or hypoxic): (1) insufficiency of uterine blood flow,[29] (2) insufficiency of umbilical blood flow,[61, 62] or (3) a decrease in maternal arterial oxygen content.[31] Other mechanisms, for example, fetal anemia or increased fetal oxygen needs (in pyrexia), are relatively rarely seen clinically.

In clinical obstetrics these three common mechanisms can be recognized during labor (that is, in the presence of uterine contractions) by various FHR patterns. Uterine contractions are thought to cause the transient decelerations because of the concomitant decrease in uterine blood flow with the contraction,[51,63] or an associated decrease in umbilical blood flow (e.g., as a result of umbilical cord compression[51]). The patterns corresponding to the above mechanisms are late decelerations, variable decelerations, and persistent fetal bradycardia.[47] A prolonged stepwise insufficiency of uterine or umbilical blood flow would likewise be recognized as a bradycardia. It has been proposed that a fetus with normal FHR variability will not revert to one with absent FHR variability caused by asphyxia during labor unless one of these asphyxial "stress" patterns is present.[47] Conversely, if the FHR variability is absent on initial application of the FHR monitor, then it is not possible to distinguish between asphyxial and nonasphyxial causes of decreased FHR variability, and the fetal stimulation test or fetal blood sampling for determination of acid-base status must be performed.

On the basis of the above considerations, a tentative definition of fetal distress is as follows: progressive fetal asphyxia that, if not corrected or circumvented, will result in decompensation of the physiologic responses (primarily redistribution of blood flow to preserve oxygenation of vital organs) and cause permanent central nervous system and other damage or death.

The clinical means by which we currently use the above definition to ensure adequate fetal compensation is by noting the progress of severity of the FHR stress patterns, and the retention of FHR variability. Intermittent or sustained decreases in FHR variability in the presence of stress patterns are assumed to signal the onset of decompensation, unless asphyxia is ruled out by ancillary testing. There may be a role for fetal blood sampling, but in the presence of normal FHR variability its role is quite limited.[64,65] It is hoped that future physiologic studies, and correlation with FHR patterns, will further refine the definition of "fetal distress" and make the diagnosis more accurate in the clinical setting.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Edward J. Quilligan, Irvine, California. In this article Drs. Parer and Livingston have attempted to define fetal distress by reviewing the fetal physiologic adaptations that occur with decreased oxygenation and serve to protect the brain, heart, and adrenals. The definition that they have developed is a logical one: progressive fetal asphyxia that, if not corrected or circumvented, will result in decompensation of the physiologic responses (primarily a redistribution of blood flow to preserve oxygenization of vital organs) and cause permanent damage to the central nervous system and other damage or death. The difficulty lies in the use of this definition clinically. We know the heart rate change is associated with a change in fetal oxygen (i.e., late, variable, or prolonged decelerations), so we can determine the first half of the definition with continuous heart rate monitoring. The authors would also like us to believe that the second half of the definition, decompensation, can be determined by examining the

heart rate variability. Although changes in heart rate variability have been shown to result from hypoxia, I am unaware of studies relating variability to decompensation.

Let us assume for a moment that they *do* reflect decompensation. Will it help clinically? Our goal is to prevent fetal death and damage without unnecessary cost to the mother. I would emphasize the latter *without unnecessary cost to the mother* because five of the seven randomized trials have demonstrated an increase in the cesarean section rate in the continuously monitored group.[1] In terms of reduction of intrapartum death, I believe continuous monitoring has accomplished that, even though the trials mentioned above do not prove it.[1] Nonrandomized trials such as the one by Dr. Yeh et al.[2] at University of Southern California do show a difference and reveal the large number of patients necessary to demonstrate this difference (about 100,000). I would agree with the authors that combining abnormal fetal heart rate pattern and fetal heart rate variability may reduce this unnecessary cesarean section rate for fetal distress, and still prevent antepartum deaths. It is in the prevention of central nervous system damage that we have difficulty. There is no good evidence in the literature that the frequency of central nervous system damage in infants is decreasing.[3] In fact, the opposite seems true. Furthermore, as the authors point out, a very small percentage of central nervous system damage is incurred during labor. When we studied infants who had cerebral palsy, there was an increased incidence of abnormal fetal heart rate patterns and absent variability, and there were fetuses in whom cerebral palsy developed without any typical fetal distress patterns.[4]

It appears to me that if we are to reduce central nervous system damage, we need additional information, such as what degree of lack of oxygen for how long causes brain damage? Although we have some information from Myers'[5] classic studies, it must be remembered that the study animals were anesthetized or heavily sedated, which may influence the brain's ability to tolerate hypoxia. To further confuse the issue, Clapp et al.[6] have shown that brain damage in fetal sheep can be caused by intermittent cord compression without fetal acidosis.

The authors have indicated the final event in fetal decompensation is the reduction in fetal brain blood flow as a result of a decrease in fetal cardiac output. It would be important to know whether the authors think if it is at this point that brain damage occurs. If so, do they see any role for the measurement of blood flow in the umbilical or carotid vessels to assist in determining this point of decompensation?

I do not mean to denegrate the role of continuous fetal heart rate monitoring in the management of labor nor the authors' explanation for the development of brain damage. I simply believe that there are a number of "blanks" in the equation at this time, before we can say we have the factual information to significantly reduce that small portion of brain damage that may occur during labor. These authors have done excellent work in helping to fill in those blanks, and I would urge them to continue their work.

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DR. ROBERT GOODLIN, Denver, Colorado. The term *heart rate variability* is one that is dear to me. I think I introduced it at this society's 1970 meeting in Hawaii and Dr. Quilligan was my official discussant.[1] Like many things that I have done, it seems to have gotten out of hand. On our labor deck, for instance, we often cannot begin oxytocin administration or do certain other procedures because somebody has decided that the fetal heart rate tracing shows decreased variability. Zalar and Quilligan[2] showed that the loss of beat-to-beat variability had no significance. I suggest that there are many papers that show that loss of beat-to-beat variability by itself is a rather useless concept.[3] I hope that the authors' article will not now carve the concept in stone so that we cannot dig ourselves out of the hole. It seems to me that if you call it *asphyxia,* you must obtain a fetal blood sample, scalp or otherwise.

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DR. PARER (Closing). Dr. Quilligan, you ask if I have solid evidence that loss of FHR variability in an appropriate setting does signify decompensation. I do not have incontrovertible, hard data yet. I think I have provided most of the physiologic data I have and little

of it is published. We have not closed the circle yet, but I accept as an article of faith that these data will become available. The reason I accept this is the wide clinical experience I had at Los Angeles County Hospital under the guidance of yourself and Dr. Hon. Since that time I have looked for exceptions to the rule "fetuses born with normal heart rate variability will have an Apgar score above 7 at 5 minutes no matter what else is going on with the heart rate." There are very few exceptions to that rule, maybe one in a thousand. When there is heart rate variability, the infants are vigorous at birth. There are more formal data available. Krebs et al., for example, conducted a study and reached similar conclusions (see reference 45). Variability was determined within approximately 30 minutes of birth and the predictability for a vigorous fetus was 98%. This is very good and holds true in the presence of late and variable deceleration.

Your second question, why the incidence of cerebral palsy has not decreased over the years despite our intensive monitoring, is a difficult one. One problem is that intrapartum asphyxia is probably responsible for <10% of all cerebral palsy. No matter how well we abolish intrapartum asphyxia as a cause of cerebral palsy, we will not alter the overall incidence much. My view on this is that intrapartum asphyxia is a potentially avoidable cause of cerebral palsy; that is why I think we should concentrate our efforts to avoid this problem.

As we mentioned in discussion of a previous paper, part of the problem with some controlled trials of fetal monitoring is that the rules for heart rate interpretation were quite different from those accepted today. Two aspects deserve mention. First, there was no emphasis on heart rate variability, and second, response times were not clearly defined. One trial required that the response time be less than 90 minutes in the case of an infant with signs of asphyxia. Now, if we say that an infant can sustain brain damage within 10 minutes, then 90 minutes is totally inappropriate. That is not the fault of electronic fetal monitoring but rather the fault of the obstetric facility that cannot intervene more quickly.

Dr. Quilligan, you mentioned a subject I want to emphasize: the degree and duration of asphyxia. There is almost certainly an interaction between duration and degree of asphyxia on the one hand and the previous condition of the fetus (whether or not it has glycogen stores or is growth retarded) on the other. The answer to these questions will quite clearly affect the relationship between asphyxia and brain damage.

Dr. Kirschbaum, you would like to call fetal distress *asphyxia* and we are not far apart on that. You also want to bring dysfunction of other organ systems into the definition and I would be delighted to do that. I agree that other organ dysfunction should ultimately be part of the overall definition of intolerable asphyxia. The difficulty is that in a clinical setting, it is difficult enough to include only the brain.

Dr. Goodlin, you pointed out that I did not emphasize sufficiently the fact that we cannot isolate loss of FHR variability. Loss of FHR variability signifies decompensation of physiologic mechanisms only in a particular setting. For simplicity, I will say that if a fetus has a loss of variability during labor in the absence of deceleration or bradycardia, you can be almost 100% sure it is not a result of asphyxia. The setting must be appropriate before you can rationally call a loss of variability the result of asphyxia.

You made another point about fetal blood sampling. If you study some of the original papers of fetal blood sampling, you will find that they have a nagging inaccuracy of 10% or 20%; that is, if you do 100 fetal blood samples on normal fetuses during labor, acidosis will be found in about 10 or 20. Thus, if you have obtained a fetal blood sample for whatever reason and proceed to act on the result, these infants at birth would be quite vigorous. The inaccuracy inherent in the interpretation of fetal blood samples far surpasses the inaccuracy in determining FHR variability. The reason is that peripheral blood, which can rapidly turn cyanotic on vasoconstriction, is being sampled. What we need is a central marker of fetal integrity. I believe that FHR variability is the best candidate for that.

A comparison of the morbidity of midforceps and cesarean delivery

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Neonatal and maternal outcome in 358 midforceps and 486 cesarean deliveries was compared by retrospective analysis. Neonatal outcome was evaluated on the basis of Apgar score, cord blood gas values, admission to the neonatal intensive care unit, and birth trauma. Maternal outcome was based on intraoperative and postoperative complications, blood loss, and hospital stay. There was no increase in significant short-term neonatal morbidity in the midforceps group, while maternal morbidity was higher in the cesarean delivery group. It is concluded that, in selected cases, midforceps delivery is safe for the neonate and mother. (Am J Obstet Gynecol 1990;162:1428-35.)

Key words: Midforceps, outcome

Considerable controversy exists as to the place of midpelvic forceps deliveries in present-day obstetric practice. Reports that indicate increased neonatal morbidity with the use of midforceps[1-4] and the availability and safety of cesarean deliveries are cited as ample reasons for abandoning the midforceps procedure.

Other reports,[5,6] however, have noted no increase in neonatal risk with midforceps delivery and also point to the increase in maternal morbidity and mortality with cesarean delivery. The reported differences are difficult to reconcile because of the multiple variables involved. The station at which the midforceps procedure was performed, gestational age, preexisting medical and obstetric problems, and the experience and skill of the operator are but a few of the factors that influence neonatal and maternal outcome. In addition, midforceps have been compared to other methods of delivery that were not appropriate alternatives.

To provide additional information as to the risk of midforceps procedures, a comparison of neonatal and maternal outcome associated with midforceps and cesarean delivery in the second stage of labor was carried out. The deliveries occurred over an 8-year period in an institution where midforceps was used regularly in the management of dystocia or fetal distress.

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Material and methods

Between Jan. 1, 1981, and Dec. 31, 1988, there were 18,469 live births at the University of California, Los Angeles, Medical Center. Of this total, 358 midforceps and 486 cesarean deliveries, which were performed during the second stage of labor for management of dystocia or fetal distress, were retrospectively analyzed for a comparative study of neonatal and maternal morbidity.

All deliveries were of a single, term fetus in a vertex presentation with a gestational age of ≥37 weeks. Specifically excluded from the study were patients with medical and obstetric problems that could affect outcome regardless of the method of delivery. These conditions included severe preeclampsia and chronic hypertension, diabetes mellitus more advanced than class B, placenta previa, and abruptio placentae. Also excluded were cases of failed midforceps and vacuum extractions.

The definition of midforceps applicable to this study was that in use before the appearance of the revised definition proposed in the American College of Obstetricians and Gynecologist Committee Opinion published in 1988. However, only those midforceps procedures involving rotation of the fetal head from an occipitotransverse or oblique occipitoposterior position at station +1, +2, or +3 (centimeters below the ischial spines) were included. Most of the oblique occipitoposterior positions were rotated to direct occipitoposterior and the infants were delivered as such. Only two midforceps deliveries were performed at a +1 station; the remainder were at +2 or +3 station. The majority of vaginal operative deliveries were performed with Kielland forceps. Only cesarean deliveries performed

with the fetal head at similar stations were included. The position of the fetal head before delivery was not tabulated for cesarean or midforceps operations performed for management of fetal distress.

The term *dystocia* was used with reference to patients with an arrest of descent and prolongation of the second stage of labor beyond 2 hours. The labor pattern before the onset of dystocia was not evaluated. All patients had continuous electronic fetal monitoring during labor. Fetal distress was diagnosed by the physician in attendance on the basis of an abnormal fetal heart rate pattern including persistent late decelerations, severe variable decelerations, or sustained bradycardia. Fetal scalp blood samples were obtained when indicated. No attempt was made to tabulate the type or severity of the abnormal fetal heart rate pattern or the degree of acidosis before delivery.

Details of the operative procedures were obtained from dictated, typewritten, operative notes, which were required on all midforceps and cesarean deliveries. Information regarding the neonate was obtained from a copy of a pediatric newborn assessment form that was contained in the mother's chart. In those instances where morbidity was recorded, the newborn's chart was reviewed in detail.

Approximately 90% of the deliveries were performed by the resident staff under the supervision of full-time faculty members. The remainder of the operations were performed by full-time or visiting faculty members on their personal private patients.

The mean and standard deviation for age, parity, birth weight, length of second stage of labor, epidural anesthesia during labor, oxytocin augmentation, and hospital days were calculated for each group. Neonatal outcome was assessed by Apgar scores, arterial and venous cord blood gas values, admission to the neonatal intensive care unit, and birth trauma. Umbilical cord blood gas values were tabulated only for the last 2 years of the study because, before that time, samples were identified merely as "cord blood" with a single pH value. During the last 2 years, complete blood gas analyses for both arterial and venous blood were available in approximately 50% of the study patients. Maternal outcome was analyzed with respect to blood loss, febrile morbidity, intrapartum and postpartum complications, and the frequency of blood transfusions. Blood loss was estimated by the change in hematocrit (percentage points) between admission and the first day post partum in nontransfused patients. Febrile morbidity referred to a temperature of ≥38° C or more that appeared after the first 24 hours post partum and necessitated antibiotic treatment. The majority of patients undergoing cesarean section received prophylactic antibiotics. Statistical significance of the differences in means was calculated with the standard t test or by Fisher exact analysis.

Table I. Primary indication for operative delivery

	Midforceps	*Cesarean delivery*
Dystocia	171*	207
Fetal distress	187	279
TOTAL	358	486

*Occipitotransverse, $n = 94$; occipitoposterior (right or left), $n = 77$

Results

The primary indication for the operative deliveries is indicated in Table I. The incidence of midforceps and cesarean section deliveries in the study group was 1.9% and 2.6%, respectively. During the same time period, the overall cesarean delivery rate was approximately 16%.

The profiles of the study populations are shown in Tables II and III.

A comparison of midforceps and cesarean section deliveries in the dystocia group (Table II) revealed differences in the means for birth weight and the duration of the second stage of labor. The use of epidural anesthesia was comparable in the two groups, but a greater percentage of patients undergoing cesarean delivery required oxytocin stimulation of labor. Parity and change in hematocrit were not significantly different between the two groups, but hospital stay was longer in the cesarean delivery group.

The differences in variables in the fetal distress group were similar to those observed in the dystocia group with the exception of the mean age of patients. Blood loss, as reflected in change in hematocrit, was greater in the cesarean delivery group.

Apgar scores ≤4 at 1 minute and <7 at 5 minutes are shown in Tables IVA and IVB. Significant differences in Apgar scores after midforceps or cesarean delivery were noted in the fetal distress group but not the dystocia group.

Data concerning umbilical cord arterial and venous blood gases are shown in Table V and VI. There are no significant differences in averaged values for pH or base excess when midforceps and cesarean deliveries are compared. However, there is a greater degree of acidemia in the fetal distress group than in the dystocia group regardless of the method of delivery. There are a greater number of neonates with pH < 7.10 in the midforceps group, compared with cesarean deliveries for management of dystocia, but differences are not significant.

Table II. Patient profile—Dystocia

	Midforceps (N = 171)	*Cesarean delivery (N = 207)*	*p Value*
Age (yr)	24.9 ± 7.0*	25.9 ± 5.0	NS
Parity	0.53 ± 1.42†	0.51 ± 0.94‡	NS
Birth weight (gm)	3507 ± 412.3	3699 ± 511.7	<0.001
Second stage of labor (min)	182.5 ± 68.5	220.7 ± 120.0	<0.001
Labor epidural (%)	65	63	NS
Oxytocin augmentation (%)	57	78	<0.001
Hospital days	2.8 ± 0.7	5.0 ± 1.4	<0.001
Change in hematocrit (%)	−6.9 ± 3.7	−7.8 ± 3.7	NS

*Mean ± SD.
†Nulliparous, 81%.
‡Nulliparous, 73%.

Table III. Patient profile—Fetal distress

	Midforceps (N = 187)	*Cesarean delivery (N = 279)*	*p Value*
Age (yr)	24.8 ± 6.5*	26.4 ± 5.7	<0.001
Parity	0.64 ± 1.08	0.79 ± 0.98	NS
Birth weight (gm)	3219.0 ± 462.9	3538.2 ± 516	<0.001
Second stage of labor (min)	52.0 ± 41.7	93.5 ± 67.2	<0.001
Labor epidural (%)	79	80	NS
Oxytocin augmentation (%)	33	64	<0.001
Hospital days	2.2 ± 0.7	5.0 ± 1.9	<0.001
Change in hematocrit (%)	−6.6 ± 4.1	−8.3 ± 2.4	<0.001

*Mean ± SD.

Table IVA. Apgar scores—Dystocia

Apgar score	*Midforceps (N = 171) (%)*	*Cesarean delivery (N = 207) (%)*	*p Value*
≤4 at 1 min	11	16	NS
<7 at 5 min	1	4	NS

Table IVB. Apgar scores—Fetal distress

Apgar score	*Midforceps (N = 187) (%)*	*Cesarean delivery (N = 279) (%)*	*p Value*
≤4 at 1 min	12	29	<0.001
<7 at 5 min	2	10	<0.001

Operative and postoperative maternal complications associated with the method of delivery are shown in Tables VII and VIII. The third- and fourth-degree extensions and uterine extensions are unique to the method of delivery and could not be compared. Febrile morbidity was significantly increased ($p < 0.001$) and the need for blood transfusions was three times greater in the cesarean delivery patients ($p < 0.001$).

The short-term neonatal complications are depicted in Table IX. There were no neonatal deaths. There were no skull fractures or seizures noted in the records. Included in the shoulder dystocia cases was one infant with a fractured clavicle. In approximately 50% of cases, admission to the neonatal intensive care unit was for observation or to rule out sepsis.

Comment

Uncertainty regarding the safety of midpelvic forceps delivery stems from conflicting reports of neonatal morbidity. Cooke[4] reported a number of serious complications including skull fracturs, seizures, and central nervous system depression in 429 midforceps deliveries. Hughey et al.[7] compared 458 midforceps deliveries with 17 cesarean section deliveries performed for similar indications and noted a 30% neonatal morbidity in the forceps group compared with 0% with cesarean section. Chiswick and James[8] reported significantly greater neonatal morbidity in neonates delivered by midforceps than in a control group who were delivered of their infants spontaneously. Bowes and Bowes[9] compared 71 midforceps deliveries and 37 cesarean sections performed because of a prolonged second stage of labor and reported 19% and 5% neonatal morbidity, respectively. Dierker et al.[5] found no evidence of greater neonatal morbidity with midforceps compared with cesarean section when the indication for delivery in both groups was dystocia or fetal distress. Traub[6] compared 132 Kielland forceps deliveries and 20 failed Kielland deliveries with 101 cesarean sections performed during the second stage of labor and could find no increase in neonatal morbidity in either forceps groups.

The reasons for the differences between these reports concern the difficulty of the midforceps deliveries and the comparison of midforceps with other routes of delivery. Older studies, which describe excessive

Table V. Umbilical cord blood gas pH

	Dystocia		*Fetal distress*	
	Arterial	*Venous*	*Arterial*	*Venous*
No. of cases	30		26	
Midforceps	7.23 ± 0.06 (<7.10 = 7%)	7.32 ± 0.10	7.19 ± 0.09 (<7.10 = 8%)	7.26 ± 0.08
No. of cases	47		36	
Cesarean delivery	7.24 ± 0.05 (<7.10 = 2%)	7.31 ± 0.05	7.17 ± 0.10 (<7.10 = 11%)	7.25 ± 0.07
p Value	NS	NS	NS	NS

Table VI. Umbilical cord blood gas base excess (mmol/L)

	Dystocia		*Fetal distress*	
	Arterial	*Venous*	*Arterial*	*Venous*
No. of cases	30		26	
Midforceps	−5.7 ± 3.2 (> −10.0 = 10%)	−4.0 ± 1.9	−8.3 ± 2.6 (> −10.0 = 15%)	−5.7 ± 2.8
No. of cases	47		36	
Cesarean delivery	−5.3 ± 3.9 (> −10.0 = 8%)	−3.5 ± 2.2	−8.4 ± 3.5 (> −10.0 = 17%)	−5.8 ± 3.2
p Value	NS	NS	NS	NS

trauma and neonatal morbidity, were associated with a high incidence of "difficult" midforceps deliveries performed at high stations, sometimes requiring multiple attempts at rotation and traction before delivery was accomplished. As a consequence, midforceps deliveries at station 0 or +1 are rarely attempted in current obstetric practice. Neonatal outcome after midforceps delivery was compared with that after other methods of delivery when there was no valid basis for comparison. A realistic comparison of midforceps delivery requires that the alternative methods of delivery be appropriate under the circumstances.

Dystocia group. The increase in the length of the second stage of labor and the high percentage of oxytocin stimulation of labor in the dystocia group are expected findings. The difference between the midforceps and cesarean delivery groups with regard to these two variables is probably of limited clinical importance. However, it is reassuring to note that the mean birth weight in the midforceps group is significantly lower than that in the cesarean section delivery group. The average length of the second stage of labor, which exceeded 3 hours, confirms the present tendency to allow the second stage to continue as long as there is no evidence of fetal distress.

Epidural anesthesia was used during labor in 65% of patients delivered by midforceps for management of dystocia. In the subgroup with transverse arrest of the fetal head, 94% underwent epidural anesthesia. Whether epidural anesthesia in labor contributes to the incidence of malposition or prolongation of the second stage of labor is unclear. Hoult et al.[10] found a fivefold increase in the use of forceps and a threefold increase in malpositions with epidural anesthesia. Johnson et al.[11] reported longer first and second stages of labor with epidural anesthesia. Friedman and Sachtleben[12] noted no increase in the frequency of malpositions or change in labor patterns with epidural anesthesia.

The anticipated difference in averaged blood loss between cesarean and vaginal deliveries was not observed probably because of additional bleeding associated with vaginal lacerations and episiotomy extensions in the midforceps group.

The condition of neonates at birth, as reflected by Apgar scores and cord blood gas values, indicates no apparent differences between the midforceps and cesarean groups. Number of hospital days was greater in patients delivered abdominally, as expected.

Fetal distress group. The significant difference in mean birth weight between the midforceps and cesarean neonates is again noted. The length of the second stage of labor was significantly less in the midforceps group than in the cesarean group. This difference and the increased percentage of low Apgar scores in the cesarean group probably results from the time required to prepare for and perform the abdominal operation. In addition, the use of general anesthesia for cesarean delivery also may have contributed to the number of low Apgar scores. A relationship between the low Apgar scores and cord blood gas values in the cesarean

Table VII. Maternal operative complications

	Midforceps (N = 358)		*Cesarean delivery (N = 486)*	
	n	%	*n*	%
Cervical-vaginal lacerations	64	18	15	3
Third-degree extension	52	14.5	0	0
Fourth-degree extension	43	12	0	0
Uterine extension	0	0	102	21
Inadvertent cystotomy	0	0	3	0.6

Table VIII. Maternal postoperative complications

	Midforceps (N = 358)		*Cesarean delivery (N = 486)*	
	n	%	*n*	%
Febrile morbidity	14	4	122	25
Pulmonary embolism	0	0	2	0.4
Deep venous thrombosis	0	0	5	1
Blood transfusion	7	2	29	6

delivery group could not be shown. The lack of correlation between Apgar scores and the metabolic state of the neonate has been noted by others.[13-15] Moreover, Dennis et al.[16] also were able to show that the acid-base status and Apgar scores in 230 term births did not correlate significantly with neurodevelopmental outcome at 4½ years. In fact, the group of children with the highest degree of impairment were in the nonacidotic, low-Apgar-score group. The authors suggested that in the fetus the ability to produce an acidosis in response to labor may be an indication of well-being.

Maternal complications. Our data support an increase in maternal morbidity with cesarean delivery compared with midforceps delivery. Specifically there was an increased incidence of febrile morbidity and the occurence of deep venous thrombosis, pulmonary embolus, and more frequent need for blood transfusion. The increased febrile morbidity was noted even though 90% of patients undergoing cesarean section received antibiotic prophylaxis, compared with 5% of midforceps delivery patients. The lacerations and extensions of incisions were generally minor in both groups but in some cases did account for the need for blood replacement. The two patients with pulmonary embolus were discharged after appropriate medical treatment.

Table IX. Neonatal short-term outcome

	Midforceps (N = 358)		*Cesarean delivery (N = 486)*	
	n	%	*n*	%
Shoulder dystocia	7	2	0	0
Cephalhematoma	14	4	0	0
Facial palsy (temporary)	14	4	0	0
Admission to neonatal intensive care unit	21	6	19	4

The future morbidity of cesarean delivery, which should be considered, includes morbidity associated with repeat cesarean delivery, repeated blood transfusions, and the risk of uterine rupture.

Short-term neonatal outcome. Midforceps delivery did result in some trauma to the neonate, but the injuries were relatively minor and transient. There were seven shoulder dystocias, including one infant with a fractured clavicle. Erb's palsy, occurring in two infants, resolved before discharge and the facial palsies also were transient. The figure for admission to the neonatal intensive care unit for both the midforceps and cesarean section groups is probably low. Information regarding this event was obtained from a copy of the newborn assessment form, which was contained in the mother's chart. If admission to the neonatal intensive care unit was not noted on the form or occurred at a time after the initial assessment, the admission would have been missed. Of the neonates who were admitted to the neonatal intensive care unit, 75% were discharged in <48 hours.

Long-term neonatal outcome. No attempt was made to perform a long-term follow-up of the neonates in this series, but the subject has been extensively reviewed by Richardson et al.[17] Fuldner[1] and Eastman et al.[2] reported an increase in the incidence of cerebral palsy after midforceps delivery while Steer and Boney[18] found no such relationship. Friedman et al.[19] reported decreased Intelligence Quotient with midforceps delivery but neither Benaron et al.,[20] Corston,[21] nor Bishop et al.[22] could confirm this relationship. Dierker et al.[23] could not find a significant difference in the incidence of neurologic deficit between midforceps and cesarean delivery peformed for management of dystocia or fetal distress.

It must be acknowledged that there are weaknesses and limitations to the retrospective design used in our study with its inherent nonrandom method of assignment. A number of factors that enter into the decision to perform midforceps or cesarean deliveries were not controlled. These include station of the fetal head, estimated fetal weight, size and shape of the maternal

pelvis, severity of fetal distress, condition of the mother, and the degree of enthusiasm of the residents and faculty members to attempt midforceps delivery. Some appreciation of the impact of these factors on the decision as to the method of delivery can be gained from the following tabulation of the incidence of midforceps deliveries in selected series: Dierker et al.,[5] 0.8%; Bowes and Bowes,[9] 1.2%; Dunlop,[24] 5.1%; Gilstrap et al.,[15] 7.3%; Danforth and Ellis,[25] 12.9%; this series, 1.9%.

Another potential weakness of our study could be that the exclusion of failed forceps deliveries obscured instances of significant trauma to the neonate or the mother. Although this possibility cannot be ruled out, Traub[6] found that neonatal outcome after failed Kielland forceps delivery was not different from outcome after successful Kielland's or cesarean delivery.

The safe use of midforceps requires a systematic approach to proper patient selection and the recognition of factors that are important in minimizing neonatal trauma. During the course of our study, an attempt was made to adhere to the following guidelines as a means of ensuring the prudent use of midforceps: (1) ascertainment of a clinically adequate pelvis without prominent ischial spines, (2) verification that the fetal head fills the hollow of the sacrum, (3) assessment of the fetal head to confirm position and the degree of deflexion or asynclitism, (4) use of adequate anesthesia, (5) presence of an individual with experience and skill in the use of midforceps, (6) application of forceps, rotation of the head, and descent with traction proceeds with ease or the procedure is abandoned, and (7) informed consent.

We conclude that the data presented in this study support the concept that midforceps delivery can be performed in carefully selected patients with no increase in significant, short-term neonatal morbidity and with a substantial decrease in maternal morbidity compared with cesarean deliveries performed under similar circumstances. We did not evalaute long-term neonatal outcome. The definition of midforceps proposed in an opinion by the Committee on Obstetrics of the American College of Obstetricians and Gynecologists published in 1988 was: "The application of forceps when the head is engaged but the leading point of the skull is above station +2." According to this definition, the present study would concern low forceps rather than midforceps, except for the two cases at +1. However, the definition is less important than the underlying principle. The use of forceps to cause rotation and downward movement of the widest part of the fetal head past the narrowest part of the maternal pelvis is a potentially hazardous procedure that should be performed with care by or under the supervision of a skilled operator. If the proposed definition removes some of the stigma associated with the use of midforceps without a loss of respect for the procedure, then the change may be appropriate.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Gilbert A. Webb, San Francisco, California. The role of the use of forceps to effect delivery when the vertex is in the midpelvis in modern obstetrics has been a subject of much controversy. This has resulted in the virtual abandonment of the procedure from many obstetric practices. Many candidates for the board examination have no cases of midforceps deliveries listed. There has been a decline in the number of individuals who are teaching the procedure.

Healy and Laufe[1] surveyed 144 members of the Association of Professors of Obstetrics and Gynecology in 1981. They found that only 18% of residency training programs felt that teaching midforceps deliveries was very important and 47% felt it was important. Unfortunately as the number of faculty capable of teaching any procedure declines, the numbers of residents who are capable of performing that procedure also decline.

Dr. Bashore and his group are to be commended for continuing the use of and the teaching of this operative technique. Dr. Bashore also is to be commended for this very careful evaluation between comparable indications for the termination of the labor process. By selecting only those patients with complete cervical dilation, when the vertex was at station 0 to +3 and was either occipitotransverse or occipitoposterior when the decision was made to deliver, he has eliminated many of the variables that have confounded previous studies.

At the point he has selected there are only two methods of delivery available—cesarean section or midforceps. The study is thus very narrowly focused. His careful analysis of his data revealed that there is no significant incidence of neonatal morbidity with either method while the maternal morbidity with cesarean section is significant. The two incidents of pulmonary embolism were potentially life-threatening. The increased use of blood transfusions also is an increased risk to the mother. The prolonged hospital stay with cesarean delivery is also signifciant in today's climate of cost cutting.

I reviewed our private practice for the year 1988. Four of the five members of our practice are members of this society and all are trained in the proper use of forceps. Out of 547 deliveries 101 (18.5%) were by cesarean section. Of this 101 21 (21%) were done for dystocia and 15 (15%) were done for management of fetal distress. These represent 2.79% and 3.83% of the total deliveries. Seventeen patients were delivered by midforceps because of fetal distress (3.10%) and 42 because of dystocia (7.67%). There was one case with an Apgar score of 3 at 1 minute and 8 at 5 minutes in the forceps delivery for fetal distress group. This was the only case in either the cesarean section or forceps group with an Apgar score of ≤4. It was related to a nuchal cord. All of our midforceps deliveries would be classified as low by the new American College of Obstetricians and Gynecologists definition.

There were no neonatal complications. The only maternal complication was urinary retention in two patients, but his cleared after 48 hours of catheter drainage.

Comparison of our data with those of Dr. Bashore is not possible as they are not as focused. All midforceps deliveries were included (under the old definition) rather than the limited group of his, but our results do reinforce the safety of the procedure when it is properly selected and executed.

There is no doubt that midforceps deliveries are operative deliveries and must be thought of as such. Respect for the procedure, as in any operative procedure, is essential. Dr. Bashore states that most of the fetuses in the occipitoposterior position were delivered in that position by use of Kielland's forceps. I would ask why rotations to anterior positions were not done either by Kielland's forceps or a Scanzoni maneuver?

In looking at the maternal complications after the midforceps deliveries, no mention was made of bladder complications, namely, hematuria or atony. I would ask Dr. Bashore if he is aware of any such problems. I noted that he had three "inadvertent cystotomies" in the cesarean section group.

The American College of Obstetricians and Gynecologists' redefinition of forceps delivers would place all but two of Dr. Bashore's deliveries in the low-forceps groups, but he is very careful to point out that the change in the definition does not decrease the need for careful selection and expert technique in effecting safe delivery.

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Dr. James Caillouette, Pasadena, California. I'd like to add a word of caution regarding morbidity statistics. Let's remember that what Dr. Bashore reported was the experience at the University of California, Los Angeles, Hospital. In my opinion policy for private practice should seldom be based on university hospital experience. To support this statement, I asked the infection control nurse at Huntington Memorial Hospital in Pasadena to tell me our infection rate for cesarean sections. Our cesarean sections show a 0.9% surgical wound infection rate. The nurse epidemiologist at the Los Angeles County–University of Southern California Medical Center told me that their current infection rate for cesarean section is 13.1%. I don't know the rate at

University of California, Los Angeles. However, I submit that university hospitals are apples and private community hospitals are oranges.

Dr. Howard Blanchette, Berkeley, California. I too am concerned about your definition of neonatal morbidity. You report one fractured humerus, 14 cephalhematomas, and 14 transient facial palsies. In the private sector there is certainly concern about "social" morbidity. You have to inform patients about these transient phenomena. Dr. Bashore, particularly with regard to facial palsy, could use of the vacuum have eliminated that component of morbidity? In our community, despite the fact that many of our obstetricians are solid practitioners with extensive experience with midforceps, there has been a rapid decline in the use of midforceps. Now virtually all use the vacuum rather than forceps for these deliveries.

Dr. Robert Goodlin, Denver, Colorado. I think we should be careful about the use of the term *failed* forceps. All of our obstetric textbooks describe this as something that should never happen. The expression should be a *trial of* forceps. I have tried over the years to teach all residents, before they become senior residents, the techniques of forceps rotation. Of the hundreds of people that I have worked with, I have yet to know one who says that out in the "real world" he still does these procedures.

Dr. Gainer Pillsbury, Long Beach, California. Dr. Goodlin, I am one of your residents who learned the use of forceps and was an enthusiast for several years. For the last 10 to 15 years, however, I have gone over to the vacuum extractor almost exclusively and find equally good results. Of course, I'm unencumbered with data to prove it, but I feel that I have equally good results with less maternal trauma.

Dr. Bashore (Closing). Dr. Webb, I suppose the tendency to rotate oblique posterior presentations to occipitoposterior ones is an institutional pecularity. The number of full-time faculty members who supervise the delivery room varies between 16 and 18 at any one time. Each has his or her own preference for a particular forceps procedure. Some posterior presentations were rotated to occipitoanterior ones by the Scanzoni maneuver and some with Kielland's forceps. Indwelling catheters were necessary after forceps rotation in some cases, but we did not tabulate the number.

Dr. Caillouette, the incidence of wound infection after cesarean section does vary between institutions. In those institutions with resident training programs and with a large percentage of nonprivate patients, there will be a higher rate of wound infection than will be noted in a private patient setting.

Dr. Blanchette, there is no doubt that facial palsy is a risk of forceps delivery, especially midforceps and especially with rotation. All of the facial palsy in our series was transient. I certainly agree with you that, had vacuum extraction been used, we probably wouldn't have had cases of facial palsy. The other side of that argument is that some of the vacuum extractions would have failed and cesarean section would have been necessary. Also it must be remembered that vacuum extraction has its own associated neonatal morbidity.

Dr. Goodlin, perhaps if we use the term *failed trial of forceps,* we would all be more correct. I'm sure that midforceps procedures are more likely to be performed in institutions with residency training programs. When residents go into private practice, the world does change. Dr. Roy Pitkin described to me a survey he performed when he was at Iowa, involving residents who had completed their training there more than 5 years previously (Pitkin RM. Personal communication). All had been trained in the use of midforceps. He asked two questions: (1) Were there indications for the use of midforceps in your obstetric practice? About 75% responsed "yes." (2) How many midforceps procedures have you done since you went into private practice? The answer was usually varied between "none" or "one" or "two." So even residents who were all trained in the use of midforceps are not using them in their private practice.

Dr. Pillsbury, I cannot resolve the question as to the use of vacuum or midforceps. This discussion will certainly continue. However, one must recognize that there is an incidence of morbidity associated with the use of the vacuum extractor.

Neonatal and maternal outcome in low-pelvic and midpelvic operative deliveries

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A retrospective analysis of low-pelvic and midpelvic operative deliveries (according to the new definitions by the American College of Obstetricians and Gynecologists, 1989) matched with cesarean section deliveries of similar station was undertaken. In all vaginally delivered groups there was significantly decreased maternal morbidity, maternal hospital stay, and estimated blood loss. In the midpelvic deliveries, there was a significant increase in the frequency of neonatal resuscitation and an increase in base deficit for the umbilical artery. In both the midforceps and low-forceps groups, there was a significant increase of neonates with cord arterial pH <7.10, and an increase of base deficit, even when cases of fetal distress were eliminated. The midforceps group also had an increased rate of admission to the intensive care nursery and an increase in the risk of significant birth trauma. In considering a midforceps or midvacuum operative delivery, the potential associated risks to the neonate must be balanced against the benefits to the mother. (Am J Obstet Gynecol 1990;162:1436-44.)

Key words: Obstetric forceps, vacuum extraction, birth injury, newborn outcome

Amid increasing parental expectations for the "perfect baby," a markedly increased cesarean section rate, and the tense medical-legal climate, the controversy surrounding the role of vaginal operative delivery in modern obstetrics continues unabated.[1, 2] Although many studies have been published regarding vaginal operative deliveries, few have used control groups, and even fewer have been prospective, randomized trials.[3] In August 1989 the Committee on Obstetrics: Maternal and Fetal Medicine of the American College of Obstetricians and Gynecologists published an opinion[4] on obstetric forceps, redefining the concept of outlet, low-pelvic and midpelvic operative vaginal delivery, within a −5 to +5 scale system of station. On the basis of this new system of station and these redefinitions of outlet and low-pelvic and midpelvic operative deliveries, neonatal and maternal outcomes were studied to clarify the risks and benefits of midpelvic and low-pelvic operative vaginal delivery.

Material and methods

Four categories (midforceps, midvacuum, low-forceps, low-vacuum) of vaginal delivery were compared with matched cesarean deliveries in each category with a second stage of labor at least 30 minutes in duration. Neonatal and maternal outcome variables were identified with the computerized perinatal data base maintained by the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California Medical Center at San Francisco, which contained 20,831 deliveries from November 1975 until December 1988.

First, the perinatal data base was adjusted to reflect the new definitions of station, which range from −5 (floating) to +5 (crowning) with the level of the ischial spines at 0, rather than the previous system of −3 to +3. The leading portion of the fetal skull now describes the level of station rather than the biparietal diameter or the caput. The data base was additionally adjusted for the new definitions of mid, low, and outlet vaginal operative deliveries by individual maternal chart review. Midoperative vaginal delivery is that in which the head is engaged, but the leading portion of the fetal skull is above a +2 station. Low operative vaginal delivery is defined as either station dependent or rotation dependent. Station dependent is when the fetal skull is at +2 station or below, with a rotation of 45 degrees or less. The rotation dependent category includes deliveries when the fetal skull is at +2 station or below, and the rotation exceeds 45 degrees. An outlet operative vaginal delivery occurs when the fetal skull is at +4 or +5 station, the scalp is visible at the introitus, and the rotation does not exceed 45 degrees.

After the perinatal data base was adjusted for the expanded definition of station and recategorization of mid, low, and outlet vaginal operative delivery, the data base was scanned for deliveries with the following cri-

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teria: singleton pregnancies, cephalic presentations, gestational age ≥37 weeks, and second stage of labor longer than 30 minutes. Cases specifically eliminated were failed forceps or failed vacuum delivered, followed by cesarean section. Maternal variables studied included maternal morbidity, duration of intrapartum and postpartum hospital stay, the rate of blood transfusions, and the estimated blood loss at delivery. Neonatal variables included admission rate to the intensive care nursery, the number of days of ventilator use, the time to achieve sustained, spontaneous respirations, the necessity for active resuscitation at birth, Apgar scores at 1 and 5 minutes, the presence of birth injury, birth weight, and umbilical arterial and venous cord gas values (pH, base excess, P_{O_2}, and P_{CO_2}). Individual neonatal chart review was undertaken to define specific birth injuries.

The cases were selected and compared as follows: midforceps ($n = 95$) and midvacuum ($n = 52$) versus cesarean section, with a second stage of labor of at least 30 minutes at similar station ($n = 290$), and low-forceps ($n = 921$) and low-vacuum ($n = 347$) versus cesarean section of similar station and second stage >30 minutes ($n = 64$). The Bird modification of the Malmström vacuum extractor was used in the majority of the operative vacuum deliveries, rather than the softer silicone rubber cup. The categoric variables between the different groups were assessed by χ^2, and the quantitative variables were contrasted by Student's t test (SPSSX).

Results

The following maternal variables were significant at values of $p < 0.001$ in each category of mid and low operative vaginal delivery (both forceps and vacuum) versus matched cesarean section: decreased estimated blood loss, decreased intrapartum and postpartum hospital stay, and decreased maternal morbidity with the vaginal operative deliveries (see Table I). There was no significant difference in the rate of administration of blood transfusions between the different groups and the matched cesarean sections. Parity differed significantly only for the midforceps subgroup in which there was an increased incidence of nulliparous women in the cesarean section group.

In terms of neonatal outcome, there was only one neonatal death in the low-forceps group; death was a result of meconium aspiration. To show significant changes in perinatal mortality associated with the different modes of delivery, the sample size must be much larger than the data base used for this study. Thus this study focuses on neonatal morbidity.

Assessment of the neonatal outcome variables revealed that active neonatal resuscitation was significantly increased in both the midvacuum and midforceps groups compared with the matched cesarean sections even when corrected for fetal distress. In the low-vacuum group there was significantly more resuscitation required in the matched cesarean section group (possibly because of more difficult extractions at cesarean section). There was no difference in the rate of resuscitation in the low-forceps group compared with the matched cesarean sections (Fig. 1).

Table I. Significant maternal outcome variables in midoperative and low-operative procedures versus matched cesarean sections*

Method	*Mean estimated blood loss at delivery (ml)*	*Mean intrapartum and postpartum hospital stay (days)*	*Maternal morbidity (%)*
Midforceps	505 ± 240	4.17 ± 2.23	25.0
Midvacuum	455 ± 155	3.62 ± 1.56	32.1
Cesarean section	828 ± 251	5.58 ± 1.84	57.1
Low-forceps	456 ± 179	3.74 ± 1.63	32.8
Low-vacuum	456 ± 294	3.74 ± 1.25	32.8
Cesarean section	753 ± 293	5.60 ± 1.60	70.3

*Comparisons at $p < 0.001$.

The rate of admission to the neonatal intensive care unit was significantly higher for midforceps deliveries (Fig. 2). Correction for fetal distress did not eliminate the increase in admissions. There was no difference in the neonatal intensive care unit admission rate when low-forceps and low-vacuum deliveries were compared with cesarean sections. There were no differences in the following neonatal variables when the vaginal operative groups were compared with cesarean sections: the amount of time to develop sustained respirations, Apgar scores at 1 and 5 minutes (categorized as <7 versus 7 to 10), or number of days of ventilator use. Umbilical cord arterial and venous blood gas values are described in Tables II, III, and IV and in Fig. 3. Significant differences in pH include a doubling in the percent of neonates with umbilical vein pH values <7.20 in the midforceps group when matched with cesarean section at similar station. There is a similar, significant increase in the percent of infants with umbilical artery pH values of <7.10 in both the midforceps and low-forceps groups. Significant differences in base excess include an increase in arterial and venous base deficit in the midforceps and midvacuum deliveries versus the cesarean sections, and an increase in arterial and venous base deficit in the low-forceps group. These differences persist when cases of fetal distress are analyzed separately.

Table V describes the percent of associated labor abnormalities of each mode of delivery (active phase arrest, slow slope active phase, prolonged labor) and the respective mean lengths of the first and second stage

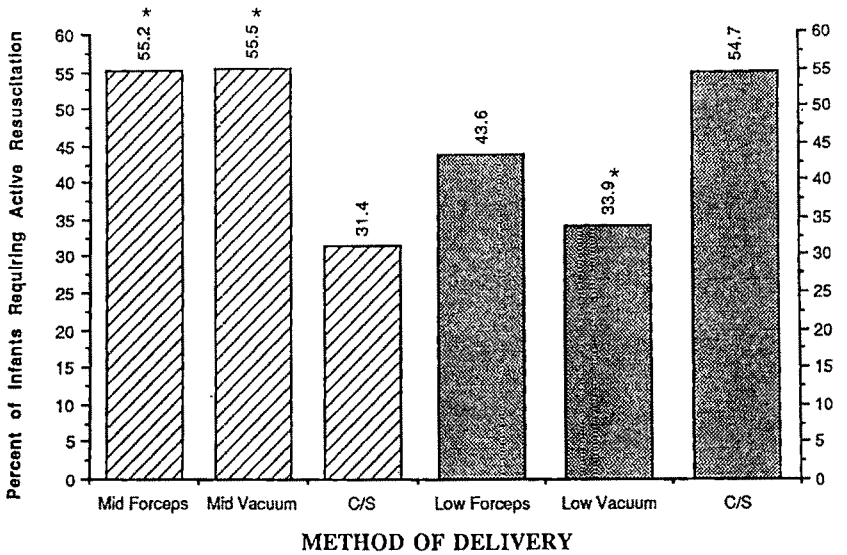


Fig. 1. Rate of active neonatal resuscitation.

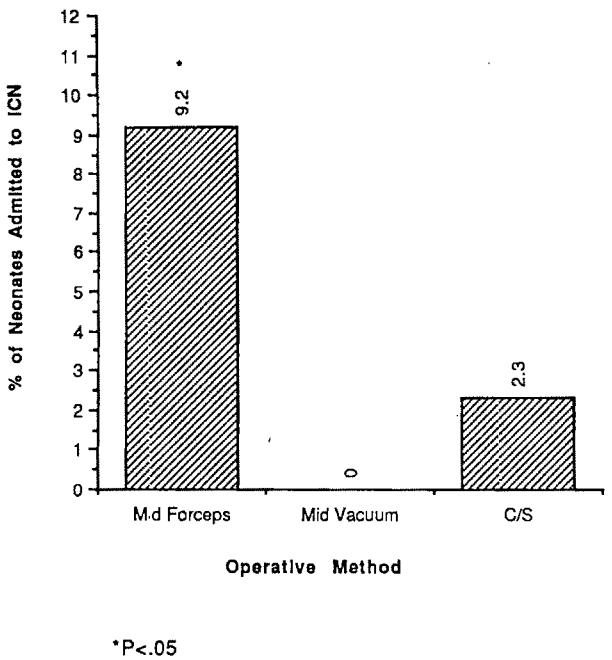


Fig. 2. Intensive care nursery admission rates for midoperative vaginal delivery corrected for fetal distress versus matched cesarean section.

of labor. Birth weights differed in two of the groups: the midforceps (3526 ± 482 vs 3642 ± 490 gm in the cesarean section group; $p < 0.05$), and low-forceps (3472 ± 461 vs 3602 ± 433 gm in the cesarean section; $p < 0.05$).

Table VI describes the incidence of birth trauma overall with the different methods of operative vaginal deliveries. Birth trauma was increased significantly in the midforceps and midvacuum deliveries compared with matched cesarean sections. However, the majority of the increased birth trauma in the midvacuum deliveries was a result of bruising. When bruising was eliminated as a category, the difference in the midvacuum category versus cesarean section disappeared. The difference in the midforceps group did persist at a $p < 0.05$ level of increased birth trauma (nerve, fracture, and significant "other"). The majority of the birth trauma with the midforceps groups was composed of nerve injury and fracture, with one additional case in the "other" category: a case of dural venous sinus thrombosis. This occurred in a case of a failed Scanzoni maneuver followed by a delivery with Kielland's forceps from an occiput posterior position at delivery. Of the 21 cumulative birth injuries, 10 were probably directly attributable to the instrument (eliminating clavicular fractures and Erb's palsies): four skull fractures, five facial nerve palsies, and one dural venous sinus thrombosis. Table VII describes the specific birth injuries according to method of operative delivery.

Comment

This retrospective study of mid and low operative vaginal deliveries matched with cesarean sections at similar stations is the first description of maternal and neonatal outcome using the newly published definitions by the Committee on Obstetrics: Maternal and Fetal Medicine of ACOG.[4]

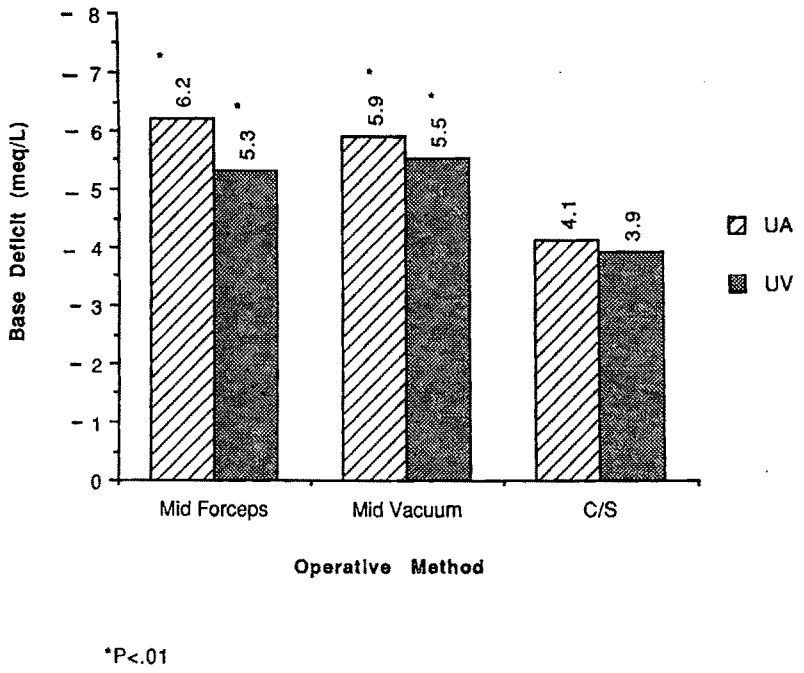


Fig. 3. Base deficit of umbilical cord gas values with midoperative vaginal delivery versus matched cesarean section.

The finding of significantly less maternal morbidity, less estimated blood loss, and decreased hospital stay with operative vaginal deliveries compared with cesarean section deliveries is in agreement with other studies.[5] In considering the operative methods separately, midforceps delivery had substantially more detrimental neonatal effects. These adverse outcomes were expressed as a significantly increased rate of admission to the intensive care nursery, an increased necessity for active neonatal resuscitation at the delivery, an increase in neonatal acidemia as reflected by increases in arterial and venous umbilical blood base deficits, and an increased risk of significant birth trauma (except from bruising). These differences are not explained by labor abnormalities or by fetal distress. In each category the matched cesarean section group had a higher incidence of active phase arrest, slow slope active phase, prolonged labor, and longer first and second stages of labor.

Midvacuum delivery also had adverse neonatal effects: an increase in resuscitation at the time of birth, an increase in arterial and venous base deficits in umbilical cord blood gases, and a significant risk of bruising from the application of the vacuum cap, which can result in an increased risk of cephalohematoma and jaundice.[6,7] In a recent publication Svenningsen[8] compared the slow pressure buildup of the vacuum with the rapid buildup, and found no significant alteration

Table II. pH of umbilical cord venous blood gases of operative vaginal deliveries versus matched cesarean sections

Method	*pH < 7.20 (%)*	*Significance*
Midforceps	34.6	$p < 0.01$
Cesarean section	15.1	—
Midvacuum	28.9	—
Cesarean section	15.1	—
Low-forceps	33.2	—
Cesarean section	22.8	—
Low-vacuum	18.8	—
Cesarean section	22.8	—

Table III. pH of umbilical cord artery blood gases of operative vaginal deliveries versus matched cesarean sections

Method	*pH < 7.10 (%)*	*Significance*
Midforceps	46.8	
Cesarean section	20.3	$p < 0.001$
Midvacuum	28.9	
Cesarean section	15.1	—
Low-forceps	41.7	
Cesarean section	26.3	$p < 0.05$
Low-vacuum	24.1	
Cesarean section	26.1	—

Table IV. Mean umbilical arterial and venous blood P_{O_2} and P_{CO_2} values according to mode of delivery

Method	*Umbilical arterial P_{O_2}*	*Umbilical venous P_{O_2}*	*Umbilical arterial P_{CO_2}*	*Umbilical venous P_{CO_2}*
Midforceps	18.70 ± 6.14*	28.97 ± 5.79	53.71 ± 9.07	41.44 ± 7.07
Midvacuum	21.60 ± 5.57*	31.30 ± 6.43*	50.54 ± 8.00	41.37 ± 5.61
Cesarean section	14.60 ± 4.67	26.92 ± 5.61	53.72 ± 7.98	42.34 ± 5.38
Low-forceps	19.51 ± 5.86*	29.85 ± 6.89	52.12 ± 8.57	41.18 ± 6.23*
Low-vacuum	20.23 ± 5.74*	29.07 ± 6.51†	53.02 ± 9.54	42.37 ± 7.39
Cesarean section	13.87 ± 5.10	25.87 ± 7.32	55.52 ± 9.20	44.60 ± 6.93

All values represented as mean ± SD.
*$p < 0.01$.
†$p \leq 0.001$.

Table V. Labor abnormalities associated with mode of delivery

Method	*Active phase arrest (%)*	*Slow slope active phase (%)*	*Prolonged labor (>20 hr) (%)*	*Persistent occipito-posterior (%)*	*Occipito-transverse (%)*	*Mean length of first stage (min)*	*Mean length of second stage (min)*
Midforceps	10.4*	13.5*	13.5*	25.6	21.1	716†	136*
Midvacuum	9.6†	23.1	17.6	13.7	15.7	743	187†
Cesarean section	25.5	29.0	28.0	27.7	19.7	835	225
Low-forceps	13.2†	12.2	13.7*	13.9	7.3*	735	133*
Low-vacuum	12.6†	17.8	17.0	14.3	10.2†	727†	164*
Cesarean section	23.4	20.3	26.6	18.8	20.3	838	195

*$p < 0.01$.
†$p < 0.05$.

Table VI. Incidence of birth trauma overall with method of operative delivery

Method	*n*	*Absence of birth trauma (%)*	*Bruising (%)*	*Other*	*Significance*
Midforceps	89	94.4	1.1	4.5	$p < 0.05$
Midvacuum	51	84.2	11.8	4.0	$p < 0.001$
Cesarean section	290	99.0	1.0	—	
Low-forceps	866	95.2	2.8	4.8	—
Low-vacuum	342	88.8	9.4	1.8	—
Cesarean section	634	98.4	1.6	—	

in the maximum force applied and a decrease in the incidence of cosmetic injury with the rapid technique.

It cannot be stated strongly enough that any attempt at midpelvic or low-pelvic vaginal operative delivery should be considered a trial and should be conducted in an environment in which an immediate cesarean section in the event of a failed procedure can be carried out, since neonatal outcome is adversely affected if there is a delay from the failed procedure to the delivery.[9] We eliminated failed forceps and failed vacuum procedures because of the difficulty of ascertaining all cases in which an attempted vaginal delivery failed. Inclusion of these cases could possibly have influenced the findings. However, it would be expected that these cases would show an even greater adverse neonatal outcome; this would only strengthen our conclusions. In contrast, the low vaginal operative birth appears to have marked maternal advantages, with little, if any, effect on neonatal outcome parameters.

Umbilical cord arterial and venous blood gas values have only recently been studied in relationship to mode of delivery. Gray and Nelson[10] describe three groups of neonates delivered by one of the following three methods: low outlet forceps without previous "mid-

pelvic forceps rotation," silicone rubber vacuum extractor with the only criteria of engagement of the fetal head and complete cervical dilation, and a group of patients who were delivered spontaneously. They found no significant differences among the groups in cord blood pH, P_{CO_2}, P_{O_2}, base excess, or bicarbonate values. Nickelson and Weber[11] found that delivery by vacuum extraction or low forceps resulted in lower pH and higher carbon dioxide tension, but that these changes were correlated with the indication for the procedure, rather than the procedure itself (i.e., when fetal distress was eliminated, there were no differences from spontaneous vaginal deliveries). It is interesting to note that in our findings of cord gas values, there was an increase in umbilical vein blood P_{O_2} in the low-vacuum and midvacuum deliveries and an increase of umbilical artery blood P_{O_2} in the midforceps and midvacuum group, despite increased acidemia in these latter groups. It is possible that this increase in P_{O_2} might be secondary to the Bohr effect (shifting of the oxygen affinity curve in the event of acidosis). Unfortunately, we did not measure oxygen saturation and thus cannot evaluate the Bohr effect. Because acidemia is associated with poor neonatal outcome, the decreased pH and increased base deficit are clinically more important findings.

The relationship of an increased base deficit reflecting fetal acidemia to encephalopathy has been described by Low et al.[12] In a study of preterm and term high-risk infants, the presence of a base deficit >30 mmol was significantly correlated with newborn encephalopathy (28% incidence, with 8% in the severe category). The long-term outcome of neonates from the different modes of operative vaginal delivery has been sporadically studied; the control group, if used at all, consists of spontaneous deliveries. Small follow-up studies of infants born by forceps[13, 14] and by vacuum[15, 16] deliveries have not shown significantly different outcomes but all studies except one[17] have been completed before the children were 6 years of age, when more subtle learning disabilities might appear.

Finally, the importance of the current ACOG schema for classifying instrumental vaginal deliveries into four rather than three categories is validated by comparison of our results with those of a previous study.[18] Our first study found no active adverse fetal effects attributable to the use of midforceps delivery (old definition). The matching technique of data analyses was identical in the two studies. Clearly, the old definitions of "low" and "mid" pelvic delivery added a large number of infants with excellent outcomes to the "mid" pelvic group, thus obscuring the true morbidity of this delivery mode. When a midvacuum or midforceps delivery is contemplated, the potential risks to the neonate must be carefully balanced against the benefits to the mother.

Table VII. Number of serious birth injuries associated with mode of delivery

Method	*Facial nerve palsy*	*Erb's palsy*	*Skull fracture*	*Clavicular fracture*
Midforceps	2	1	1	0
Midvacuum	0	1	0	0
Low-forceps	3	3	2	5
Low-vacuum	0	1	1	1

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. John J. Molitor, Fullerton, California. The proper role and use of the obstetric forceps has been in contention since they were introduced, approximately 300 years ago. The pendulum of opinion has swung from one extreme to the other and is rarely in equilibrium. The literature is full of conflicting reports; some say midforceps are dangerous, others say they are not and that they still have a place in obstetrics. When neonatal outcome in midforceps deliveries is studied, one sees that most of the older studies are flawed because they were done before the widespread use of electronic fetal monitoring; thus there was no way to know the true condition of the infant before the midforceps delivery was used. In addition, there were no controls in the older studies. More recently, studies of this problem have matched the operative vaginal deliveries with cesarean section deliveries for similar indications. This study specifically matches operative vaginal deliveries with section deliveries, station for station, according to the new ACOG definitions. When I, and all of you who are my age received our obstetrics training, midforceps delivery was defined as delivery from 0 station down. Even if the head was almost on the perineum and if it was more than 45 degrees off the anteroposterior diameter of the pelvis, the delivery became by definition a midforceps delivery and was so coded on the chart. This was an impossibly large category, including simple forceps deliveries and those of great difficulty requiring consummate skill; all were classified as midforceps. In reality, most of the difficult operations resided in the fraction when the station of the head was between 0 and +2. With the new definitions, those deliveries are classifed as midforceps and the easier ones at lower station, even if requiring rotation up to 45 degrees, are classified as low-forceps.

Each time the obstetrician has to terminate a labor that is not progressing well, for whatever reason, he or she must make the decision to deliver vaginally or abdominally. This is always a judgment call and can be easy or extraordinarily difficult. Cesarean section is the "easy way out" but frequently does not serve the mother as well as a vaginal delivery would.

The data from this study show that cesarean section delivery imposed greater blood loss, longer hospital stay, and increased maternal morbidity when compared with operative vaginal delivery. I think estimated blood loss is extremely unreliable and subjective and that it is more likely to be underestimated in the case of a vaginal delivery than for cesarean section. In any event, there was no difference in the transfusion rates of the two groups. The length of stay figures are higher for both vaginally delivered and cesarean section patients than what we see here in southern California. I am surprised at the high morbidity rate of 70.3% of the mothers who had cesarean deliveries matched with the low-forceps and vacuum deliveries. I would like to ask Dr. Laros if this figure reflects just mild elevations of temperature or clinically significant infections? All of the above notwithstanding, I do not think those figures indicate that the mothers suffered any serious consequences of having a cesarean section rather than a vaginal delivery. What is more important, especially in today's litigious climate, is the welfare of the infants. The study figures show a significant increase in the frequency of neonatal resuscitation and an increase in umbilical artery base deficit for the midpelvic deliveries. In both the midforceps and low-forceps groups, there was a significant increase in the number of neonates with cord arterial pH <7.10 and an increase of base deficit. We have no long-term follow-up data on those infants and I leave to the experts whether or not this degree of acidemia would have any serious long-term effects. What bothers me most is the increased rate of admission to the intensive care nursery for the midforceps group and the increased risk of significant birth trauma for both the midforceps and low-forceps groups. Even though the incidence is different in the two groups, there are still traumatic injuries in the low vaginal delivery category as well as in the mid category. To the parents, traumatic injuries to the infant cannot be wished away, cannot be explained away as not statistically significant; they literally cannot be defended. If you ask any mother undergoing a labor that becomes complicated and requires a decision regarding method of delivery, she will tell you, "Doctor, do what is best for my baby." She will say this even though there may be some increase in risk to her own welfare. The most apprehensive mothers I have dealt with throughout the years are schoolteachers who work with developmentally disabled and handicapped children. As a father of a son with Down syndrome, I can appreciate their concern. The majority of available clinical evidence today shows that midforceps use exposes the fetus to harm.[1, 2] This study, in my opinion, corroborates that view even with the new definitions of the college. In the search for a newly defined category of "safe" forceps deliveries, I do not think you can balance the risks to the infant against the benefits to the mother; they are just too disproportionate.

The current incidence of midforceps deliveries as shown by papers presented here do not provide adequate numbers for training residents in this procedure. Furthermore, the risk to the infant does not justify more midforceps deliveries for training purposes.

It is time to acknowledge that midforceps delivery should be a thing of the past and that any forceps delivery, except perhaps outlet forceps by the new definition, should be approached with great caution.

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DR. ROBERT A. SACK, Coarsegold, California. This year's program contains a paper discussing vaginal birth after cesarean section, another compares outcome in midforceps delivery and cesarean sections, and a third compares outcome in low-forceps and midforceps deliveries. These three papers, like so many in the recent literature, are directed toward reduction of the ever-increasing cesarean section rate. But do we really want to go back to the "good old days?" To attempt to answer this question, a paper presented before this society 21 years ago is now resurrected.

This was the study of maternal, obstetric, fetal, and newborn characteristics (including a long-term pediatric follow-up) of 766 infants who weighed 10 pounds or more at birth.

Admittedly, macrosomic infants represent less than 50,000 of the newborns delivered each year in this country; but these cases may serve to remind us of the mayhem committed in an effort to maintain a "respectable" cesarean section rate.

In this study the two major maternal complications were postpartum hemorrhage and shoulder dystocia. Seventy-eight mothers (10.3%) received at least one 500 ml transfusion of whole blood. Shoulder dystocia occurred in 76 deliveries (10.0%) and was lethal to the newborn in 29% of the cases. There was one maternal death.

One hundred fourteen (16%) of the infants were severely depressed at birth, all were apneic and required endotracheal intubation and artificial respiration for 2 to 60 minutes. Thirty-nine fetal deaths occurred (10 antepartum and 29 intrapartum). Sixteen infants were live-born but died in the nursery; the perinatal mortality rate was 7.2%.

Twenty-three (11.4%) of the 200 survivors who were followed up for an average of 5 years had a disabling neurologic problem. Nine (4.5%) died before the age of 7; six died in the first year of life.

A review of labor characteristics reveals that 39% of the mothers had a first stage of labor <6 hours and 87% had a first stage less than 13 hours. There was a second stage of labor less than 1 hour in 92% of cases.

Methods of delivery were as follows: spontaneous vertex, 76%; low-forceps, 6%; primary cesarean section, 5.2%; midforceps, 5.2%; and breech extraction, 2.8%. There were four destructive operations, two version and extractions, and one postmortem cesarean section.

As can be seen, almost every operative delivery known was used in the delivery of these unfortunate infants. I am certain that some methods are as foreign to the recently trained obstetrician as the Voorhees bag. They, and their patients, should be thankful.

One paper on this year's program refers to a prolonged second stage of labor and another refers to a second stage longer than 30 minutes. It might prove enlightening to evaluate the 8% of cases with a prolonged second stage in this series. In the 62 patients with a second stage longer than 1 hour, the following occurred: there were 22 cases of shoulder dystocia and nine infants died during delivery. There were three stillbirths, two destructive operations, and one death in the nursery as a result of sepsis. In this subset of cases there was a 26% perinatal mortality rate.

The study just presented was not done at the turn of the century. Unfortunately, I and a fair number of you in this audience, contributed to these statistics. In many training programs today a cesarean section may be the only operative delivery the residents are adequately trained to perform. To emphasize this fact, the report from the University of California Los Angeles notes 325 midforceps deliveries in 8 years. This number represents barely three such cases each month, and this number is not adequate to train a resident staff in the art of midforceps deliveries.

When the majority of residents leave training programs to enter private practice of obstetrics they are comfortable with and well trained in the performance of a cesarean section. This method of operative delivery is easy, safe, convenient and offers, by far, the least malpractice exposure.

The danger of the encouragement by consumer groups and organized obstetrics for vaginal birth after cesarean section may force some obstetricians into catastrophic situations they are not trained to handle. Two such examples would be the emergent need to perform a cesarean hysterectomy, bilateral hypogastric artery ligation, or both.

If, as is often intimated, cesarean sections are performed to increase the obstetrician's financial reward, there is a simple solution to the problem. On a relative value scale for obstetric delivery you need only to adjust the fee to reflect the degree of difficulty and the time expended. Vaginal deliveries would be paid 100% of scale, primary cesarean sections 75%, and repeat cesarean sections 50%. This plan is a sound one since it would eventually reduce physician charges but it would have little or no effect on decreasing the number of cesarean sections.

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DR. DUNCAN NEILSON, Portland, Oregon. When we review the history of forceps development, we need to include the most recent development, one in the late twentieth century. In the late 1960s and early 1970s Dr. Leonard Laufe wrote extensively about reducing the morbidity of forceps operations.[1] He developed an instrument, now called the Laufe forceps, that significantly and measurably decreased the compression force on the fetal head. Those who teach residents to perform midforceps deliveries should read Laufe's

writings and teach the use of his instrument. My partners and I have found that it greatly facilitates the operation. I think this instrument can reduce the incidence of facial palsy. We simply do not encounter this problem, which is related to compression of the fetal head, in the infants delivered by midforceps any longer.

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DR. JAMES CAILLOUETTE, Pasadena, California. Dr. Joseph Bolivar De Lee (1869-1942) championed managed labor with episiotomy and forceps delivery in an effort to achieve a perfect outcome. Let me quote a paragraph from a paper he read at the forty-fifth annual meeting of the American Gynecological Society, May 1920, which appeared in the first issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY that year.[1]

> Perhaps lacerations, prolapse, and all the evils women in labor are subject to, are, in fact, natural to labor and therefore normal, in the same way as the death of the mother salmon and the death of the male bee in copulation are natural and normal. If you adopt this view, I have no ground to stand on, but if you believe that a woman after delivery should be as healthy, as well as anatomically perfect, as she was before, and that the child should be undamaged, then you would have to agree with me that labor is pathogenic, because experience has proved such ideal results exceedingly rare.

The authors are to be commended for encouraging operative obstetrics. However, in my opinion the use of midforceps was an appropriate procedure in the early and mid twentieth century. Today the procedures of choice are low forceps and cesarean section.

To quote George Santayana (1863-1952), a contemporary of De Lee, "Those who fail to learn from the past are condemned to repeat it."[2]

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DR. LAROS (Closing). The comment regarding estimated blood loss is certainly well taken. We did study the difference between the discharge and the admission hematocrit because this reflects blood loss. There is a difference and, as we all know, the difference is greater with cesarean section. We all underestimate blood loss regardless of the route of delivery. I agree with the comments on morbidity. Although the maternal morbidity is higher with cesarean section, it is usually not of long-lasting clinical significance. Conversely, I recall an unfortunate experience during my residency, a repeat cesarean section on a young woman who developed a pulmonary embolus and died 3 weeks after delivery. She continues to remind me that whenever you operate on anyone you present them with some risk.

The birth trauma issue truly is the major one. Having examined the data, we are now going back to the data set and attempting to "tease out" those factors that lead to significant fetal trauma. We hope to be able to identify those fetuses at risk and thus avoid traumatic injuries.

With respect to our teaching philosophy, I no longer teach midforceps delivery because I think that, except in certain instances of fetal distress, one should do a cesarean section rather than a midforceps or vacuum delivery from 0 or +1 station. However, I do take the advantage of the frequent use of epidural anesthesia to gain experience with low and outlet vaginal delivery. The house officer can learn all the techniques of proper application, ascertainment of position, and the proper method of extraction. As the house officer's experience grows, he or she becomes progressively more comfortable with forceps or vacuum extraction at higher stations. I frequently will say to a patient who has been pushing 2 to 3 hours and is still in an occipitoposterior position at +3 or +4 station, "Aren't you getting tired?" Many of them say "Yes." This situation provides an ideal opportunity to learn to use these techniques. Using these opportunities allows one to feel comfortable in an emergency situation to perform a truly indicated, emergency midforceps or midvacuum delivery.

Dr. Sack, I was impressed by your article when it was published. I have not knowingly delivered a patient whose infant weighed over 4500 gm vaginally since that time. This is a philosophy that we debate and consider on our service, but I'm very concerned about the risk of macrosomia. However, I carry in my head the thought that unfortunately two thirds of the cases of shoulder dystocia will come from infants under 4500 gm, so we are not safe, but certainly we can avoid these most difficult of situations.

Dr. Neilson, I have read Dr. Laufe's work and I apologize for not giving him credit. I learned to use Simpson forceps. Dr. Wilson, my teacher, allowed us to use only one kind of forceps—Simpson's. That was true also for breech cases. After you became proficient at delivering the aftercoming head with Simpson forceps, he might allow you to use Piper's forceps.

The placenta in the litigation process

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The placenta accurately reflects many important prenatal events. It is therefore important that it be examined. This is especially useful in cases of possible future litigation, the "bad-baby cases." There is much experience now that pathologic findings in the placenta often have a decisive role in the accurate disposition of legal cases. This presentation describes the examination of the placenta and provides a brief review of the nature of placental lesions that most often impact cases of alleged malpractice. (Am J Obstet Gynecol 1990;162:1445-50.)

Key words: Placental examination, placenta and litigation

It is commonplace that the frequency of litigation regarding purported malpractice has increased. This has had a significant influence on the practice of obstetrics. The adverse effects vary widely from state to state. In addition to practitioners, medical students may have been influenced in seeking specialties other than obstetrics, for fear of future litigation.[1] It has been stated that 73% of fellows of the American College of Obstetricians and Gynecologists has had at least one lawsuit brought against them.[2]

One of the commonest reasons for litigation is an unexpected bad outcome of an infant, especially infants afflicted with cerebral palsy and those that die in the perinatal period. Inasmuch as cerebral palsy has no uniform cause, there is much room for argument in the courts as to possible deviations from the standards of practice or regarding true malpractice in the causation of cerebral palsy. Furthermore, many lawsuits are brought years after the birth of an afflicted child. This frequently makes it difficult to reconstruct accurately what the standards of practice were at the time of the child's delivery. It is often also impossible to ascertain disease factors, other than possible perinatal asphyxia, that may have had a role in the development of the neurologic disorder. For instance, possible prenatal infection with rubella virus, cytomegalovirus, or toxoplasma may be impossible to decide positively at a later date. Often, then, the witness is asked for his/her "best medical judgment," and the process is not necessarily interested in a statement of all the facts.

In addition to these vagaries, the expert witness is faced with the environment of the courtroom, to which few physicians are accustomed. This includes possible harassment by lawyers, endless postponements in courts, countless telephone calls, the review of voluminous records, and many more aggravations. The oft-asked plaintiff lawyer's question: "And how much do you charge for this testimony, doctor?" is also frequently sufficient reason for many well-meaning expert witnesses to withdraw from the whole scene altogether. This is much to be regretted, for he/she may have the only real answer to given questions—if indeed the process was seeking the real truth. But, to many of us, the legal proceedings are often executed much like a game, rather than as an honest search for the relevant facts. This is also frequently embodied in the nature of questions asked on the witness stand. And these may be unnerving, even raise one's anger.

Perinatal care is complex. It has greatly improved in recent years. Much new insight has been gained from chemical tests (such as maternal serum α-fetoprotein, human placental lactogen, amniocentesis); ultrasonography has ably displaced nearly all roentgenography of the fetus and is widely practiced with ever-improved machinery; neonatal care, resuscitation, and other measures have vastly changed over the years. One would think that cerebral palsy would have disappeared; it might, were it not such a complex disease.[3] An answer to the many questions this disease has raised was sought in a multihospital collaborative study of the 1960s. No simple cause was uncovered; in fact, the disease became perhaps more complex with this study. Thus Naeye and Peters[4] found that *chronic* rather than *acute* hypoxia, as is often suspected, has the greater influence on abnormal brain development. Similar findings have come from other studies, some of which clearly indicate that fetal brain damage may precede labor.[5, 6]

We have long maintained that a meaningful, thorough study of the placenta has much to offer in the understanding of perinatal illness.[7] Indeed, it has been my recommendation that all placentas should be ex-

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amined, at least macroscopically, and that a record should be made of all placentas. Indeed, one may consider a technician's help to undertake this task. Since the rediscovery of the frequency of a single umbilical artery, most hospitals now require at least an entry into the maternal chart as to the number of vessels in the cord; a small beginning. But there is much other information to be had from a placental examination. In my view, the placenta is a reasonably good indicator of the maternal history, often a better one than can be obtained from the common "no prenatal care" admissions patient who is cared for in so many of our hospitals. It must be a knowledgeable examination, to be sure.[8]

During the course of the last 10 years, since malpractice lawsuits against obstetricians have increased so remarkably, I have often been asked to look at the record and histologic slides of placental examinations in cases of afflicted children. This has frequently been of material help in assessing the nature of the illness and in suggesting a possible cause of the disease. It has provided, at times, the deciding argument in complex cases. It is no wonder then that I still advocate a routine placental examination be undertaken.

Placental examination

A macroscopic placental examination takes only a few minutes, and when it is routinely practiced, the examiner becomes quickly familiar with the salient macroscopic findings. Several guides have been published to aid the novice.[9, 10] The examination is ideally done at the time of delivery, and the findings are then recorded in the patient's chart. When this is not feasible, the placenta should be stored until it has become certain that the infant has done well, usually 2 to 3 days. Storage is best undertaken in a labeled ice cream container, which is then refrigerated, not frozen. The morphologic features are well preserved for many days in such conditions, although some fluid loss occurs and the thickness of the organ decreases. I have found it most practical to store the placentas in a large refrigerator whose shelves are labeled with days of the week. As the refrigerator fills, the shelf of the previous week's day is emptied. We have never missed an important specimen in this way; it has always been available when the neonatologist requested an examination because of less than optimal outcome.

All placentas in cases of multiple births, congenital anomalies, children who are small for gestational age, or complicated and premature deliveries should be routinely studied. The selection of those that warrant histologic diagnosis requires experience and the cooperation of the local pathologist. It has also been my experience that availability of a good photograph of the placenta often would have provided crucial information when only a poor description was made. This is especially the case in placentas of multiple births.

The macroscopic examination should include the measurement of length of the umbilical cord, as well as its site of insertion; a verification of the presence of three umbilical vessels; an assessment of the membranes' color and of the sheen of the fetal surface; an assessment of the color shade of the villous tissue; an inspection for fetal vascular thrombi; an estimate of the percentage of infarction; an inspection for retroplacental or retromembranous clots; and, if possible, determination of placental weight (minus membranes and umbilical cord). In multiple gestation the cords should be labeled as to the sequence of delivery (A, B, etc.), the position of cords should be stated, the "dividing membranes" should be studied, and the nature of interfetal anastomoses (if present) must be identified. It is usually best to make a sketch of twin placentas.

Findings

It has been my experience, in cases of litigation for perinatal death and cerebral palsy, that placental examination has been most beneficial when the placentas were associated with: (1) multiple pregnancy, (2) prolonged pregnancy (especially relating to meconium staining), or (3) premature delivery and small-for-gestational infants.

Major additional positive findings to explain poor fetal outcome may include vascular thromboses, abruptio placentae, a single umbilical artery, abnormal cord insertion, the presence of many nucleated red blood cells in fetal vessels, chronic villitis, or maternal floor infarction. In many such cases the lack of a placental examination would have seriously impaired an accurate judgment in some litigations with poor fetal outcome.

Multiple pregnancy. Placentas in cases of twins have one of these configurations (higher multiples may have admixed chorionic status). In instances of a single cavity the placenta is monoamniotic, monochorionic (MoMo). In instances of two cavities the placenta is (1) diamniotic, monochorionic (DiMo) (always fused); (b) diamniotic, dichorionic, fused (DiDi); or (c) diamniotic, dichorionic, separated (DiDi).

A majority of dichorionic twins are dizygotic, and most of these gestations come to near term. Dichorionic twins have significantly fewer obstetric problems than monochorionic twin gestations. The really problematic cases have usually been monochorionic (DiMo or MoMo) twins. They are all monozygotic (identical).[11] Furthermore, because the excessive mortality of monochorionic twins relates to placental vascular connections, the surface vasculature must be accurately assessed. Also important is the recording of cord insertions (velamentous-marginal cords are much more common in multiple pregnancy). Finally, the possible

presence of "vanished twin" cavities or fetus papyraceus should be ascertained, as they may be an indication of earlier pregnancy disturbance.

One frequently arising question in litigation is whether a set of twins was afflicted with the transfusion syndrome. The classic twin transfusion syndrome is a very specific entity,[12] and it is easily supported by placental findings. Controversy still exists as to the best diagnostic parameters in this syndrome. It is often the cause of premature delivery, as a result of the hydramnios in the recipient's cavity. The arteriovenous anastomosis that is responsible for the syndrome is best recognized by careful injection of the vascular tree. Perhaps because of this syndrome, or for other reasons, monochorionic twins have a known relationship to prenatally acquired cerebral lesions.[13] One other aspect of great medicolegal importance is the influence that prenatal death of one twin has on the survivor, especially when the twins are interconnected by placental vascular anastomoses. Several cases of cerebral palsy in the survivor of monozygotic twins have been described after the original description of a neonate with widespread thrombotic lesions.[14] The mechanism of this phenomenon is not yet clearly understood. It is possible that thromboplastin from the dead twin infuses into the survivor, thereby initiating disseminated intravascular coagulation. We have also seen cases in which the inescapable conclusion was that placental emboli caused infarcts in the fetus. Alternatively, the sudden loss of "counterpressure" from the dead twin may lead to temporary near-exsanguination of the chorioangiopagous survivor, with consequent hypotension and possible central nervous system damage. In any case such placental evidence is of great importance, not only for our understanding of prenatal life but also for the proper adjudication in court. Massive shifts of blood from one twin to another often have been witnessed at delivery.

Prolonged pregnancy. In my experience, litigation of cerebral palsy cases involves postmature pregnancies more often than term infants. In such cases the question of meconium aspiration or the mere presence of meconium at labor is most commonly the pivotal argument. I have opined that green meconium is the "red flag" for plaintiff lawyers but that the cause of meconium discharge is poorly understood. It hardly ever seems to make an impression when I state that I have had to perform many autopsies on stillborn, term babies, dead of asphyxia, whose death was not accompanied by meconium discharge. Also, in my routine study of *all* placentas, more than 17% are meconium stained, while cerebral palsy occurs only rarely. Meconium is discharged by mature fetuses primarily as the result of a matured endocrine system; motilin seems to be a principal agent for its production.[15] Usher et al.[16] found that meconium discharge is more importantly related to maturity than to distress. It is probable, mainly for these reasons, that meconium discharge is much more common in postmature pregnancies than at term. It is extremely rare that premature gestations are associated with meconium discharge. When the membranes are green, this is generally due to the deposition of hematoidin, which has similar spectral absorption bands and which is often combined with hemosiderin. It should also be noted that, after prolonged meconium discharge, the pigment changes color, often becoming brownish.

Because meconium has played such a major role in litigation and because the timing of its discharge has been held to be of such importance, we have attempted to find out if time of discharge could be determined from the degree of staining.[17] Meconium can be ascertained grossly, and its bilirubin content can be seen microscopically in the macrophages of amnion and chorion. We found that within 1 hour yellow-stained macrophages appear in amnion and that it takes at least 3 hours before such staining reaches the chorion. This provides an approximate timetable, but it is of little real help in critical court cases. It has never before been appreciated that meconium, while perhaps occasionally discharged *because* of asphyxia, may in itself be a toxic substance. Pathologists see degenerative changes in the amniotic epithelium soon after meconium has been discharged, but when its vascular effects were studied in perfusion experiments of umbilical cords, it was found that meconium had a profound vasocontractile effect.[18] Thus meconium discharge is complex. It may follow asphyxia but does not necessarily do so. Once discharged, it may become a cause of further prenatal oxygen restriction because of the vasoactive factors.

Premature delivery and small-for-gestational-age infants. Cerebral palsy is more common in prematurely delivered infants. In part, this is due to a much greater frequency of cerebral hemorrhages in premature infants; however, it may also be the result of the complex causes that initiate premature delivery. A major finding in the placentas of spontaneous deliveries between 20 and 30 weeks of gestation is chorioamnionitis. The amniotic sac infection syndrome may be caused by many microorganisms; the pus may be aspirated, and fetal pneumonia and sepsis are frequent results. Good evidence is accumulating that ascending placental infection causes labor, is frequently present before rupture of membranes, and may have a devastating impact on fetal well-being. Much depends on the nature of the offending organism, infection with group B β-hemolytic streptococci being one of the most serious complications of perinatal life. Not only is fetal infection of potentially devastating consequence in postnatal life, but evidence is accumulating that inflammation of the umbilical vessels per se may cause their contraction

and thus perhaps reduce placental venous return.[19] In some infections, notably group B streptococci, it is equally possible that the bacterial toxins, rather than inflammatory cells, cause vasocontraction. Inflammation of membranes and cord is readily apparent by placental examination. Moreover, superficial mural thrombosis of fetal vessels is a frequent and important concomitant.

Growth retardation, not to be confused with prematurity, may have a specific placental cause that is also best identified by placental study. Thus the maternal vascular lesions of preeclampsia and the similar lesions caused by the presence of lupus anticoagulant may significantly reduce fetal growth. Maternal floor infarction[20] is an uncommon but often repetitive cause of severe fetal growth retardation that can be ascertained only by placental study. The cause of this disease has remained elusive, as has the cause of most instances of the much commoner "chronic villitis of unknown etiology."[21] Nevertheless, these are important placental lesions that necessitate the study of this tissue. Finally, fetal surface vessel thrombi are much more common than is generally appreciated. Their cause often remains undetermined, but they clearly indicate some antenatal disturbance that may have as much significance for fetal development as is now obvious for the finding of a single umbilical artery.

Many more pertinent findings come from expert placental examination, too numerous for this brief review. I will mention only the identification of nucleated red blood cells, the anemia that is grossly visible as pallor and that may be due to transplacental hemorrhage, the presence of chorangiosis (testifying to prolonged fetal problems),[22] and many more lesions that have excellent correlation with perinatal asphyxia and with events that often long precede delivery. They should be sufficient to mandate that placental examination be practiced more routinely.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. JAMES A MERRILL, Seattle, Washington. The placenta is a human organ with an entire life span of approximately 9 months. During this time it functions as an enzyme factory, an organ of internal secretion, and an organ of transfer for the growth and developmental needs of the fetus. The importance of placental function in fetal development is well recognized. It is reasonable to expect the placenta to reflect both maternal and fetal disease states, yet the placenta is usually discarded after delivery—occasionally looked at but rarely examined in a careful manner. Dr. Fredrick (Fritz) Irving, anonymous author of ribald ballads and Professor of Obstetrics at Harvard Medical School, is quoted as remarking: "I have looked at thousands of placentas but have never examined one."

While many abnormalities of the placenta have been described, including the developmental and aging changes, interest in pathologic conditions of the placenta has not been overwhelming, and today still too little is known of the relationship of many placental lesions to fetal development and welfare. This is not

something that lends itself to planned prospective experiments. Moreover it is difficult to know if observed placental changes precede or follow adverse events in the fetus. Dr. Benirschke previously has stressed the importance of careful scrutiny of what he calls "the experiments of nature." Data are increasing to confirm that many neonatal neurologic disabilities have their origins antenatally, well before the onset of labor.

Dr. Benirschke recommends that placentas be examined routinely and, if not, that all placentas be stored, not frozen, for subsequent examination if the infant does not do well. Viewed from the perspective of personal interest and training, I certainly agree with this recommendation. Moreover, since the examination ideally is done at the time of delivery, I do not believe it is unreasonable to expect the obstetrician to accomplish a careful gross examination of the placenta and to record it in some organized fashion. Weight and measurements are important. Since intelligent examination must include adequate clinical data, the obstetrician has an advantage over the pathologist. I regret the deemphasis of pathology training. I believe that education in both gross and microscopic pathology of the placenta should be included in residency training. The practice of careful examination of the placenta in the delivery room may yield clinically helpful information such as a missing cotyledon or the presence of a succenturiate lobe, a fresh retroplacental clot of abruptio placentae, membrane rupture at the margin of the placenta (confirming the diagnosis of low implantation), significant infarcts, or even a rare chorioangioma.

Some authors have suggested, in lieu of routine examination of all placentas, that any obstetric or medical complication of pregnancy and fetal or newborn abnormality constitutes an indication for pathologic examination of the placenta. Dr. Benirschke singled out only a few complications and indicated that the selection of placentas for histologic diagnosis requires experience. Would he expand on specific indications for histologic examination of the placenta, if not routinely done?

Although desirable, there are some problems with routine pathologic examination of all placentas. The most obvious is cost. The majority of patients, those who are delivered of healthy babies, would be asked to bear an increased cost. This would not be the first example of cost for preventive and defensive medicine, however, and is less expensive than some of our new technologies. Another problem is the paucity of interested pathologists. In my experience few surgical pathologists have the training or the interest to examine many placentas. How can this be changed? Further, I see a need for greater investigation of the correlation between placental abnormality and perinatal abnormalities and outcome. For example, how good is the correlation between the finding of chorangiomatosis and fetal hypoxemia or other stress? What about hemorrhagic endovasculitis? To the extent that we can, it is important to correlate the structural and morphologic features of the placenta with perinatal loss, morbidity, and abnormal placental physiologic characteristics. At a time when every baby born is expected to be a perfect baby, this takes on new importance!

I thank Dr. Benirschke for offering a clear presentation of a topic that warrants our thoughtful concern.

Dr. Theodore Loring, Eureka, California. As an individual involved with a mutual insurance company, I find this subject dear to my heart. Dr. Benirschke, please comment on the work by Dr. Sanders from Michigan State, on what he called endovasculitis of the placenta.[1] Unfortunately, his material was published in a pathology journal and most of us in obstetrics have not had an opportunity to see it. Please also comment on the extensive work on the placenta by Dr. Naeye[2] from the University of Pennsylvania. For awhile, the companies insuring obstetricians were very pleased and hoped that the changes described by these two investigators could assist them in defending cases involving brain-damaged infants. However, I have heard nothing about their work for some time.

Dr. Merrill noted that one of our problems is that in very very few areas do we have anyone who would know anything about the placenta. My company is attempting to do something about this by urging all of our insured, some 500 or 600 people, to save a piece of the placenta and a portion of the cord with blood in it in any case where the Apgar score is under 9. We hope that perhaps we can come up with information that can help us with the defense of cases involving brain-damaged infants.

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Dr. Russell Laros, San Francisco, California. Dr. Benirschke, I was very interested in your comments about the anastomotic vessels and have a three-part question. (1) When one has a set of monochorionic twins with the intrauterine death of one twin, how frequently does the survivor become affected by disseminated intravascular coagulation? (2) When this occurs, knowledge of the time available is of critical importance to the perinatologist caring for these patients. How wide is the window of opportunity for intervention? (3) How does the clinician decide when the survivor is truly at risk?

Dr. Benirschke (Closing). Dr. Merrill, yes, indeed, I think the placenta is underevaluated. It is very difficult to anticipate what pathologists will actually do because they do not have the patience to find out what is normal. It is easy for a pathologist to learn what normal skin is. He sees skin and skin diseases all day long. He will not ever see the variations of the normal breast or placenta. They all look different, and to understand what is a truly meaningful abnormality re-

quires that one see a lot of normal cases. That is the main reason why, when a placenta is sent for evaluation, the pathologist sends back a diagnosis of a mature placenta. He doesn't really know what it is and he doesn't have the patience to go through the thick stack of books that we have written to find out. It is important that the obstetrician examine the placenta in the delivery room and communicate to the pathologist what to look for.

Which placentas should be chosen for microscopy? Placentas of babies that have poor outcomes should be. Those of severely premature babies should be also because of the frequent finding of infection. I personally think all twin placentas should be examined microscopically. Is that, perhaps, asking too much? We have about 5000 deliveries a year now at University Hospital and I do between three and five microscopic examinations of placentas each week. That's not a very large number of placentas for a pathologist to look at and he would gain knowledge quickly.

It is easy to make a photographic record of the placenta in the delivery room by taking a Polaroid photograph and placing it in the record. This is much better, particularly in the case of twins, than a poorly written description of where the umbilical cord was inserted.

Dr. Loring, and I think also Dr. Merrill, mentioned endovasculitis. I don't believe endovasculitis exists. It is a nonentity in my opinion. There have been very good articles written on systematic degeneration of the endothelium and intermixing of blood with the vascular wall in placental explants in vitro. This is a phenomenon that occurs after fetal death. When the baby dies, the vessels of the placenta disintegrate and come to look like the description of endovasculitis. The reason you don't hear much about it anymore is that it doesn't exist.

Dr. Laros, I don't know the proportion of cases with disseminated intravascular coagulation. When there are large anastomoses and one twin dies, as many as 10% to 20% have this phenomenon. A hundred years ago, one of the famous Siamese twins Chang and Eng was alcoholic and the other was not. The former contracted bronchial pneumonia and wanted to sit up while his twin wanted to lie down. Chang died and Eng said "I'm going to die too" and, almost immediately, he died. At autopsy, done in Philadelphia, there were large anastomoses noted between the twins but there was no systematic investigation of this finding. In the future, perhaps, flow velocimetry will tell us something of the umbilical cords in circumstances when one twin dies and the other survives. We should be alerted to make the diagnosis of anastomosis of surface vessels by flow velocimetry. It is very difficult to ascertain on the placental surface but you can do it in the umbilical cord if you are skilled. We will be able to see changes in the flow pattern of a baby who survives. In my opinion the degenerative event is almost immediate. It takes but an hour or two. The question I will be asked soon, as an expert witness in court, is, "If the doctor had done a cesarean section as the patient came in, would the other twin not have suffered?" Perhaps the damage would be not as much, but the disseminated intravascular coagulation event would have taken place. Recording the hematocrit in those twins with massive shifts, I think, is important. It is important for us to learn how long it takes for a 2000 gm baby to have a shift of hematocrit from 50% to 30% or 20%. How long does it take for the blood to thin? We don't know yet whether we can judge from the hematocrit the length of time elapsed before the hemorrhagic event took place.

I don't know which babies are at risk. We never see this problem in diamniotic-dichorionic twins. We never see it when one umbilical cord is so twisted that no reflux of the other baby's "bad blood" is possible. We don't see it when there is a knot in the umbilical cord. It is possible, in some cases, to anticipate it. In the future we should learn how to classify the dividing membranes clearly and to separate the diamniotic-dichorionic placentas, which are at no risk, from the diamniotic-monochorionic placentas, which are at risk. There is a magnificent piece of work going on at Utah that will be published soon. Dr. Julian De Lia has successfully done laser fulguration of connecting blood vessels between monochorionic twins with the transfusion syndrome in three cases.[1] There was immediate cessation of hydramnios and the other abnormal events. You can anticipate that we will be able to coagulate vessels and prevent this syndrome from appearing.

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Hysterectomy: A medical-legal perspective, 1975 to 1985

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Since 1975 the crisis in professional liability has been the most important problem affecting the future of obstetrics and gynecology. Increasing numbers of physicians have stopped delivering babies and most obstetricians have decreased their high-risk obstetrics. Most of the attention in the specialty has been directed toward the liability problem in obstetrics as opposed to gynecology. The liability problem in gynecology is not insignificant, however, and has increased in importance in the last several years. This is particularly true in the areas of failure to diagnose and complications of surgery. This study reports on the closed cases involving hysterectomy from Norcal Mutual Insurance Company, a physician-owned mutual company founded in Northern California in 1975. A number of factors are analyzed in comparing those cases involving payment of money because of a settlement or loss at trial with those cases in which no money was paid. (Am J Obstet Gynecol 1990;162:1451-8.)

Key words: Hysterectomy, malpractice, standard of care

The malpractice crisis is now 15 years old. Since 1974, we have witnessed a dramatic increase in liability insurance premiums for obstetrician-gynecologists. We have also witnessed the profound effect the crisis has had on the physician-patient relationship, often turning it into an adversarial nightmare.

A direct result of this crisis is the large insurance premium obstetrician-gynecologists now must pay. In 1975 many insurance companies stopped writing malpractice insurance policies, and in California physicians were faced with the prospect of being unable to buy liability insurance at any cost. A number of physician-owned mutual insurance companies were started at that time. One of these, which focused on the Northern California market, was Norcal Mutual Insurance Company (Norcal). The company has been successful and is now marketing in Southern California and Oregon.

Professional liability is the most serious problem facing the practice of obstetrics and gynecology. It has been responsible for increasing numbers of physicians seeking early retirement, dropping obstetric practice, and reducing high-risk care. A total of 73% of obstetrician-gynecologists have had at least one professional liability suit filed against them according to a survey conducted by the American College of Obstetricians and Gynecologists.[1]

Much of the emphasis on risk reduction in obstetrics and gynecology has been focused on obstetric practice with its long exposure and potential for high awards. Less attention has been aimed at the gynecologic aspects of practice that have risk potential for lawsuits. The fact that hysterectomy is one of the most commonly performed operations in the United States means that there is a significant potential for lawsuits—a fact that has certainly been noted in the legal literature.[2] This report evaluates the Norcal experience with hysterectomy-related malpractice claims. The impact of "standard of care" and other factors on the likelihood and amount of recovery is determined.

Methods

All closed claims involving hysterectomy for gynecologic indications were reviewed. The time period covered by this report is 1975 to 1985. Cases involving hysterectomy for obstetric complications, i.e., intractable hemorrhage, were excluded. Also excluded were hysterectomy claims related to complications of elective abortion.

The data were collected on a questionnaire developed to be used with a closed-claim master file. Typically, a closed-claim file consists of the pertinent hospital and office records, narrative statements of the defendant, as well as other involved health care personnel, expert and peer reviews, investigator's reports, attorney summaries, deposition summaries, and outcome reports. The completed case summaries included information on patient characteristics, third-party payor, location of venue, preoperative diagnosis, consent to surgery, and treatment alternatives used. Information was collected on the operative procedure, complications, pathologic results, and postoperative course. Data also were gathered on any injury, subsequent readmission and/or reoperation, degree of disability, and whether the injury was temporary or permanent. Finally, data were collected on the lawsuit itself, including the

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Table I. Severity of injury summary

Scale	*Definition*	*Examples*	*No. of cases*
1	Emotional		0
2	Insignificant	Leg numbness	5
3	Minor temporary	Vesicovaginal fistula Retained sponge	34
4	Major temporary	Bowel injury, ureteral injury	21
5	Minor permanent	Postoperative pain	9
6	Major permanent	Unnecessary operation	12
7	Grave	Cerebrovascular accident	1
8	Death		5
TOTAL			87

Table II. Injury summary

Cctegory of injury	*No. of cases*
Urinary injury	37
Unnecessary hysterectomy	15
Hemorrhage with reoperation	5
Bowel injury	5
Death	5
Nerve injury	4
Infections	4
Pain	3
Suture complications	2
Ovarian complications	2
Retained sponge	2
Bovie burn	1
Short vagina	1
Cerebrovascular accident	1
TOTAL	87

amount of award or settlement and the cost to the company to defend the suit.

The overall appropriateness of care and its contribution to the mishap were evaluated. Particular attention was given to the evaluation of the county medical society medical review audit committee and to the evaluations of expert witnesses and claims reviewers. In the few cases where those reports were not available, I made an assessment of the appropriateness of care (I have substantial claims and peer review experience). Appropriate care was defined as that meeting the standard of practice for the prudent gynecologist in California. Inappropriate care was defined as that falling below the standard of practice. Care was judged inappropriate if the consent was not documented, if alternative therapies should have been tried and were not, if consultation should have been obtained and was not, and if complications occurred and were not fully documented in the chart and the patient informed.

Each claim was assigned a severity of injury score based on the company's eight-point scale. This scale rates each claim from 1 (no injury) to 8 (death). Values 1 to 3 represent minor, nondisabling, temporary injuries. Value 4 is a major but temporary injury; 5 and 6 are permanent injuries, and 7 is a grave injury. Table I lists each severity category with an example and the number of cases in each category.

A total of 262 claims involving hysterectomy were available for review. After obstetrics-related claims, abortion-related claims, and claims that were not yet closed were eliminated, 87 cases remained for review and they form the basis for this report.

Results

A summary of the frequency of allegation or injury is presented in Table II. Urinary injury generated 37 lawsuits, with alleged unnecessary hysterectomy the next most frequent with 15 cases. Of particular note is the fact that five cases resulted in the patient's death.

An obstetrician-gynecologist was the surgeon in 79 of the cases (90.8%) and was board certified in 65 of those 79 (82.3%). Of the remaining eight cases, five were performed by a general surgeon and three by a family physician with major surgery privileges. No gynecologist was involved in any of those eight cases.

Thirty-four of the 87 (39%) lawsuits resulted in an out-of-court settlement or jury award to the plaintiff. Patients under 30 years old received payment in 58% of cases; 36% of patients aged 30 to 49 received payment. Patients on welfare accounted for 30 of the 87 claims (34.5%),and 12 of them received payment (32.5%). Fifty-seven patients had other insurance or were self-insured, and 22 lawsuits were successful, about the same percent as for the welfare patients.

The likelihood of payment to a patient was greater if the standard of care was not met (Table III). Overall, the standard of care was judged to have been met in 59 of the 87 cases (67%). Of the 28 cases in which the standard of care was not met, 20 received payment (71%). Eight received no payment even though the standard of care was not met. Conversely, in the 59 cases where appropriate care was rendered, 14 patients received payment (23%). A total of 77% of patients treated appropriately who filed lawsuits received no payment.

The amount of payment to the patient depended on age, severity of injury, and appropriateness of care (Table IV). Patients under 30 years old received an average payment of $101,600, with a range from $6000 to $250,000. Patients aged 30 to 49 received an average of $46,900, with a range from $1000 to $250,000. Thus payment was likely to be higher if the patient was under 30 years old when the lawsuit was filed. Two large settlements ($250,000) for unnecessary hysterectomy in young patients influenced this finding.

As shown in Table V, payment increased with severity of injury. In category 2 (insignificant injury) one of five

patients received payments. An amount of $125,000 was paid in settlement to a 32-year-old multiparous woman who alleged unnecessary hysterectomy. This case is discussed later.

Of the 34 patients in category 3 (minor temporary injuries) 10 received money. The average payment was $11,386, with a range from $1000 (to a patient with a retained sponge that was removed abdominally immediately after a vaginal hysterectomy) to $29,999 (to a patient who suffered a rectovaginal fistula that was subsequently successfully repaired). In eight of these 10 cases the care was judged to be appropriate.

The average payment for a major temporary injury (category 4) was $45,431, with a range of $15,000 to $175,000. Eleven of the 21 patients received payment. Ten of 11 cases in this category resulted in payment of <$55,000. Only in three of the 11 cases was the care judged to be appropriate.

In category 5 (minor permanent injury) (nine cases) three payments of $29,999, $50,000, and $175,000 were made, for an average of $85,000. One of these cases met the standard of care.

Major permanent injuries (category 6) (12 cases) resulted in payment in five cases. The average was $112,440 and the range was $2200 to $250,000. Four of the five cases involved allegations of unnecessary hysterectomy. Two of the five met the standard of care. Two $250,000 cases were in this category, involving in each case a hysterectomy in a young woman.

In category 7 (grave injury) there was only one patient. This patient suffered a cerebrovascular accident postoperatively. Care was judged appropriate and no money was paid.

The five cases with death all received money (Table VI). The average payment was $127,000 with a range of $40,000 to $250,000. The standard of care was met in one of the five. The care in that case was judged appropriate both by the local society medical review audit committee and by the chairman of a respected teaching program in California. The case was settled for a $40,000 payment to the estate of a 33-year-old patient who suffered a series of seizures of undiagnosed cause on postoperative day 1 and died the next day.

All of the other four cases were judged to fall below the standard of care. The $250,000 settlement was made in the case of a 39-year-old obese woman who underwent a difficult hysterectomy and Marshall-Marchetti-Krantz procedure. She was noted to be anuric immediately postoperatively, but a substantial delay occurred before a diagnosis of bilateral ureteral ligation and severe intraabdominal hemorrhage. The patient also aspirated at the start of the second operation as the surgeon removed the dressings and sutures before intubation. She died shortly after completion of the second operation.

Table III. Standard of care and compensation summary

Standard of care	*% of Patients compensated*	*% of Patients not compensated*
Met	23	77
Not met	71	29

Table IV. Patient's age and compensation in lawsuits lost or settled

Age of patient (yr)	*Average compensation*	*Range of compensation*
<30	$101,600	$6,000-$250,000
30-49	$46,900	$1,000-$250,000

A $210,000 settlement was awarded to the estate of a 41-year-old woman who underwent vaginal hysterectomy and anterior and posterior colporrhaphy for treatment of urinary stress incontinence and uterine prolapse, followed immediately by an abdominoplasty performed by a plastic surgeon. Shortly after operation the patient went into shock. The gynecologist did not assess the patient until several hours after the initial telephone call from the hospital. On reoperation, the abdomen was filled with blood. A lacerated spleen of unknown cause was diagnosed; splenectomy was performed, and the patient did not recover. An additional $110,000 was paid on behalf of the plastic surgeon.

The fourth case resulting in death was settled for $75,000. The patient was a 55-year-old obese smoker with numerous medical problems who was a poor operative candidate. In 1983 she underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for treatment of carcinoma in situ of the cervix without a preoperative medical evaluation. The surgeon was a board-certified family physician. The patient suffered major blood loss at surgery, had a cardiac arrest on postoperative day 1, and died.

The final death occurred in a 58-year-old woman who underwent abdominal hysterectomy and a Marshall-Marchetti-Krantz procedure for treatment of stress incontinence. She weighed 292 pounds, and no preoperative medical evaluation was performed. The surgeon was a board-certified obstetrician-gynecologist. The assistant was an ophthalmologist who had never assisted on an abdominal operation. Anesthesia was induced by a family practitioner with no formal anesthesia training. The patient bled to death on the operating table. The case was settled for $60,000. No urologic evaluation had been performed in any of the patients operated on for treatment of urinary stress incontinence.

Payment to the patient also varied by the appropri-

Table V. Severity of injury, compensation, and standard of care summary

Severity of injury	*No. of patients compensated*	*Standard of care met*	*Average compensation*	*Range of compensation*
Emotional	0			
Insignificant	1	1	$125,000	
Minor-temporary	10	8 of 10	$11,386	$1,000-$29,999
Major-temporary	11	3 of 11	$45,931	$15,000-$175,000
Minor-permanent	3	1 of 3	$85,000	$29,999-$175,000
Major-permanent	4	2 of 5	$112,440	$2,200-$250,000
Grave	0			
Death	5	1 of 5	$127,000	$40,000-$250,000

Table VI. Cases resulting in death

Age (yr)	*Preoperative diagnosis*	*Operation performed*	*Complication*	*Amount of compensation*	*Cost to defend*	*Standard of care*	*Outcome*
33	Urinary stress incontinence	Vag. hyst. A&P repair	Seizures on postoperative day 1	$40,000	$23,209	Met	Settled
39	Urinary stress incontinence	TAH MMK	Bilat. ureteral ligation Hemorrhage Aspiration Obesity	$250,000	$45,000	Not met	Settled
41	Urinary stress incontinence	Vag. hyst. A&P repair Abdominal pain	Hemorrhage Lacerated spleen	$210,000; $110,000	$20,366	Not met	Settled
55	Cervical carcinoma in situ	TAH BSO	Hemorrhage Cardiac arrest Obesity	$75,000	$17,924	Not met	Settled
58	Urinary stress incontinence	TAH MMK	Hemorrhage Obesity	$60,000	$15,612	Not met	Settled

Vag. hyst., Vaginal hysterectomy; *A&P repair,* anterior and posterior colporrhaphy; *TAH,* total abdominal hysterectomy; *MMK,* Marshall-Marchetti-Krantz procedure; *BSO,* bilateral salpingo-oophorectomy.

ateness of care. In those cases where care was judged appropriate and payment was made, the average payment was $26,657 with a range of $1000 to $175,000. When care was judged inappropriate and payment was made, the average was $82,982 with a range of $1866 to $250,000.

One can also look at payment by allegation or injury sustained (Table VII). Bowel injuries accounted for three settlements. The average was $36,500 with a range of $29,500 to $50,000. Of five postoperative bleeding cases, excluding the death, only one cost money. It was settled for $1866. The two cases involving retained sponges were settled for $1000 and $10,000, respectively. The cases of death have been discussed. The two largest categories are urinary injury and alleged unnecessary hysterectomy. Fifteen of 37 cases of urinary injury (37%) resulted in payment to the patient. The average payment was $36,500, the range from $6000 to $175,000. Ten of these 15 cases settled below the California reporting limit of $30,000.

If unnecessary hysterectomy was alleged, payment was made in seven of 15 cases (46.7%). The average payment in this category was $122,000, with a range of $2200 to $250,000. Only two cases settled for <$30,000.

A total of 29 of 87 lawsuits (33%) were resolved by the company with defense costs of <$1000. A total of 26 cases were dropped after a lawsuit had been filed at an average cost to the company of $632. Seventeen cases were dismissed at an average cost of $5469. The 32 cases that were settled cost an average of $16,400 to defend. The one arbitration case cost $12,459 to defend successfully. The 11 cases that were tried cost an average of $37,000. Norcal spent $2,809,139 to pay for settlement and jury award in the 34 lawsuits where the patients received money. $1,935,650 was spent by Norcal to defend the 87 cases.

Comment

A total of 17% of the cases were based on an allegation of unnecessary hysterectomy. Seven of these 15 cases resulted in payment to the patient (Table VIII). The amount of payment was related to the age of the patient. Two cases are illustrative.

A 21-year-old nulliparous woman underwent laparotomy for management of suspected appendicitis. The surgeon, a family practitioner, saw pus at operation and diagnosed pelvic inflammatory disease. There was no abscess formation. The surgeon did a total abdominal hysterectomy and bilateral salpingo-oophorectomy. No

Table VII. Payment by type of injury to patient

Injury	*No. of cases*	*No. paid*	*Average settlement*	*Range of settlement*
Urinary	37	15	$36,500	$6,000-$175,000
Unnecessary	15	7	$122,000	$2,200-$250,000
Hemorrhage	5	1	$1,866	
Bowel	5	3	$36,500	$29,500-$50,000
Death	5	5	$107,000	$40,000-$250,000
Nerve	4	1	$10,000	
Infectious	4	0		
Pain	3	0		
Suture complication	2	0		
Ovarian complication	2	0		
Retained sponge	2	2	$5,500	$1,000-$10,000
Bovie burn	1	0		
Short vagina	1	0		
Cerebrovascular accident	1	0		
TOTAL	87	34		

Table VIII. Unnecessary hysterectomy alleged

Age (yr)	*Preoperative diagnosis*	*Informed consent documented*	*Abnormality confirmed*	*Amount of compensation*	*Cost of defend*	*Standard of care*	*Outcome*
20	Cervical carcinoma in situ	No	No	$250,000	$15,947	Not met	Settled
21	Appendicitis	No	Yes	$250,000	$47,789	Not met	Trial; verdict for plaintiff
26	Chronic pelvic inflammatory disease	Yes	Minimal	$170,000	$11,131	Not met	Settled
32	Chronic pelvic inflammatory disease	No	No	$125,000	$35,714	Not met	Settled
33	Adenomyosis	Yes	No	$2,200	$11,537	Met	Settled
36	Endometriosis	Yes	No	$50,000	$36,207	Not met	Settled
38	Leiomyoma	Yes	Yes	$7,000	$40,000	Met	Settled to avoid trial after arbitration for defense

consent for this procedure was documented. A jury awarded the patient $250,000.

A 32-year-old nulliparous woman underwent exploratory laparoscopy because of pelvic pain. The board-certified obstetrician-gynecologist suspected endometriosis at laparoscopy and proceeded immediately to total abdominal hysterectomy and bilateral salpingo-oophorectomy. No consent for the hysterectomy had been documented. Only normal tissue was noted on the pathology report. The lawsuit was settled for $125,000.

In four of these seven cases operation was done because of pelvic pain. None had documentation of alternative therapies having been tried. Three of the seven had no documentation of informed consent. Four had only normal tissue noted on the pathology report. Of the total of 34 cases in which payment was made, three cases cost $250,000 and two of those were in the unnecessary hysterectomy category. Clearly, gynecologists who plan or anticipate hysterectomy, especially in a woman under age 30, must be mindful of alternative therapies and must be explicit about documentation of informed consent.

The hysterectomies that resulted in death were also educational. Four of the five were preventable. In each of the four, serious errors in judgment occurred. The two very obese patients (>250 pounds) who were operated on for management of urinary stress incontinence should have had better preoperative evaluations and other therapies tried until sufficient weight loss occurred to make the operation less risky. Significant delays in recognizing and treating immediate postoperative complications occurred in two patients. Three of the four were extremely obese. None of the four had an indication for hysterectomy for which an acceptable alternative was not available.

The issue of cost to the company to defend these lawsuits is also of interest. In a few cases it appeared that a suitable settlement to the patient at very little expense to the company was achieved. It is also clear, as anticipated, that it is much more expensive to try a case than settle it. An average of $37,000 was spent to try the cases as opposed to $16,100 to settle. The numbers are small, but in this study, surprisingly, it was cheaper to try a case and win than to lose (an average

of $24,530 vs $34,213). Perhaps in difficult cases additional monies are spent on expert witnesses or attorney's time. Finally, it would appear that few cases ultimately go to court. If they do, the outcome for the physician-defendant is good. In 9 of 11 trials, the defendant prevailed.

Of all hysterectomies done in the United States 65% are performed on women aged 30 to 49; 12% are performed on women under age 30.[3] In this study 65% of operations were indeed performed on women aged 30 to 49, but 22% were on women under age 30. One can conclude that the risk of lawsuit is substantial when a hysterectomy is performed on a patient under age 30. Again, this emphasizes the need for careful consideration before elective hysterectomy is recommended to a woman under 30.

As mentioned, there were eight cases in which the standard of care was not met, yet the patient received no payment. Five of these cases were dropped, two were dismissed, and one was tried and a defense verdict obtained. Five of the eight had no documentation of informed consent. Four of the eight involved urinary injuries that subsequently were successfully repaired. Seven of the eight occurred in rural areas of Northern California. Only in the one case that went to trial did the plaintiff's attorney make any attempt to prosecute the case.

In summary, the standard of care significantly influences the likelihood and amount of payment to the patient. If care was below standard, 71% of cases received payment. However, if the care was appropriate, 23% of cases still resulted in payment to the patient. Second, in 59 of 87 cases (67%), the standard of care was met and yet a lawsuit was filed and closed. Therefore the filing of a lawsuit does not imply substandard care.

It is increasingly clear that the current tort-based system does a poor job of separating bad outcomes where there is no breach in the standard of care from those cases where an error was clearly made. We must continue to search for a fairer way to compensate the injured patient.

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Discussion

Dr. Theodore W. Loring, Eureka, California. Dr. Whitelaw has provided us with an overview of the professional liability problems that have been caused by hysterectomies. It is a timely article; while it is economic and not scientific in nature, I think that it is as important to our specialty as any of the scientific articles being presented at this meeting.

He has reviewed the liability claims experienced by physicians insured by the Norcal Mutual Insurance Company during the years 1975 to 1985. The vast majority of the involved physicians were board-certified obstetricians who were in practice in Northern California. During this time the company experienced 262 hysterectomy claims, but only 87 of the closed cases with gynecologic indications for hysterectomy were reviewed.

Dr. Whitelaw has provided us with a detailed analysis of the cases and the problems that developed to cause the litigation. He has reviewed the procedures used by Norcal in evaluating the cases before making a decision to settle or defend. In contrast to policy of the commercial companies, physician review and input play a great part in the final decisions made by physician-owned companies. The injury summary in the author's Table II reveals that urinary tract injuries produced 37% of the cases, and unnecessary hysterectomies, the next most frequent, resulted in 17.2% of litigation. He rightly points out that the indemnity and expense costs to the company vary because of many factors.

The high proportion of urinary tract injuries and unnecessary hysterectomies in the Norcal series, although surprising, seems to be a major factor in other companies. Private data provided me by a large physician-owned company tends to confirm the Norcal data. In their claims experience from 1975 to 1985, involving both abdominal and vaginal hysterectomies in a much larger series of 312 cases, urinary tract injuries caused approximately the same percentage of claims.

The Physician Insurers Association of America, the national organization representing 42 physician-owned companies, has started a cooperative data-sharing system in which most of the companies are participating. The study from 1985 to 1988 shows that the most frequent iatrogenic injury that occurred in 809 closed files involving hysterectomy was urinary tract injury (36.7% of the cases). Obviously the neurologically impared newborn engenders the most severe type of claim. However, hysterectomy claims represent a significant portion of the files. The average indemnity paid was $80,324 for abdominal hysterectomy and $66,894 for vaginal hysterectomy for an overall average indemnity of $77,818. In this series hysterectomy cases accounted for 9% of all obstetrics and gynecology claims.

While these facts are distressing, it is important to remember that, when there is no deviation from the accepted standard of care, the jury usually will render a verdict in favor of the defendant physician. A recent national study, done by the American Bar Foundation, reveals that the plantiff success rate for 1981 to 1985 for all civil jury verdicts was 58.4%; for medical malpractice jury verdicts, 28.0%; and for obstetrics and

gynecology jury verdicts, 10%. Plaintiff success verdicts tend to vary with the severity and permanency of the injury and to some degree with where the case occurs. From the same study, the plantiff success rate in obstetrics and gynecology cases in Los Angeles County was 37.5% while in San Francisco County it was 25%.

Professional liability, often inappropriately labeled *malpractice,* has bedeviled all physicians *regardless of their specialty* or *indeed their recognized competence.* It has been with us almost since Adam and Eve. In the original minutes of the formation of the Medical Society of Humboldt County (California), a small society, organized on February 20, 1886, there is a reference to malpractice. The minutes state: "The Society should on all occasions stand by any member who should be arraigned on such a charge unless the member's action was totally indefensible." It was also agreed that the organization would spare no efforts to discourage the levying of "blood money" by means of malpractice suits, and at the discretion of the majority of the total membership such patients might be denied future care from physician members. As early as July 1, 1909, the members of the Medical Society of California could become members of an Indemnity Defense Fund. The Medical Society of the State of New York was formed in 1806, and one finds references to medical malpractice even in its early publications.

It is generally stated that professional liability is much worse today than in the "good old days," especially on our specialty. No longer can anything less than a perfect result in patient care, be considered an act of God, as in the "good old days." Malpractice litigation has profoundly affected our professional lives and our checkbooks.

We are unhappy with the tort system as a means of handling this problem, but in reality there is no alternative on the horizon. The problem could be much worse. A study by the California Medical Association and the California Hospital Association suggests that 1 in 20 hospitalized patients experiences some medical error that could produce a potential compensatory injury. In the United States this could produce at least 1,715,000 claims but only about 10% of patients actually file claims.

Unfortunately maloccurrences and indeed malpractice will continue to occur, and there will always be a few unhappy patients as long as we practice medicine. Most of the physician-owned companies have instituted claims-prevention education programs for their insured, and to date this seems to be having a positive effect on this problem.

I compliment Dr. Whitelaw on his very detailed review of the hysterectomy-liability problem and have one question to ask him. What does he see as alternatives to the tort system?

Dr. Keith Russell, Los Angeles, California. Dr. Whitelaw's article emphasizes several important points. However, a study of closed claims is deceiving in many ways because there are so many nonmedical factors that enter into the closing process—the skills of the attorneys, the position of the carriers, and the selection of juries, for instance. If you review closed claims retrospectively, you will find many in which the medical aspects are of less importance in the closing than these other factors. Dr. Whitelaw pointed this out by citing eight cases in which medical care was definitely below the standard and yet, for various reasons, no money was paid out. The medicolegal world is often entirely different from the world of medical practice. A leading attorney for the California Medical Association describes a malpractice trial as a drama in which we play roles. Review of closed claims points out only some of the factors that may enter into this courtroom drama.

We hear daily about high-risk obstetrics but seldom about high-risk gynecology. Dr. Whitelaw's report points out that three of the five deaths were associated with severe obesity. The obese patient is a high-risk gynecology patient, but many of our colleagues, I find, operate on such patients as "routine" cases. It is mandatory that for these cases we have adequate preoperative evaluation, skilled assistants, skilled anesthesiologists, and careful postoperative care including the use of pulsating thromboelastographic stockings and possibly the use of heparin. That the obese patient cannot be treated as an ordinary surgical case needs to be emphasized.

The medicolegal risk of hysterectomy is minor compared to the risk of failure to diagnose or properly manage diseases of the breast. In the national insurance registry of the Association of Doctor Owned Insurance Companies, breast cases far exceed other gynecologic cases.

Dr. Whitelaw, you mention reviews by medical review audit committees. At one time we thought the answer to some of our litigation problems was to have our peers review our cases and tell us how to defend them, yet in most medicolegal cases that mechanism either is not implemented at all or plays little role in the eventual outcome. I would like to know your feelings regarding medical review audit committees. I am part-time consultant for one privately owned and two doctor-owned insurance companies in Southern California. I find these so-called review committees have very little role when the attorneys begin to discuss the case.

Of the 87 closed cases, Dr. Whitelaw, how many were closed by jury action and how many were settled by the carriers or other parties? I suspect that something like 90% were settled and 10% decided by juries. It is encouraging that, of the cases involving obstetrician-gynecologists that have gone to a jury in California in the last 15 years, roughly 65% are found for the defense (the doctor or the hospital) and only 35% for the plaintiff. I believe that Dr. Whitelaw's figures will show that also. Doctors involved in a malpractice action often say "Well, I don't want to settle the case because that's an admission of malpractice. I don't feel that there was any malpractice." From a financial standpoint, however, it is often more economical for the physician's insurer to settle than it is to go to court, even though the physician has a two out of three chance of winning the case.

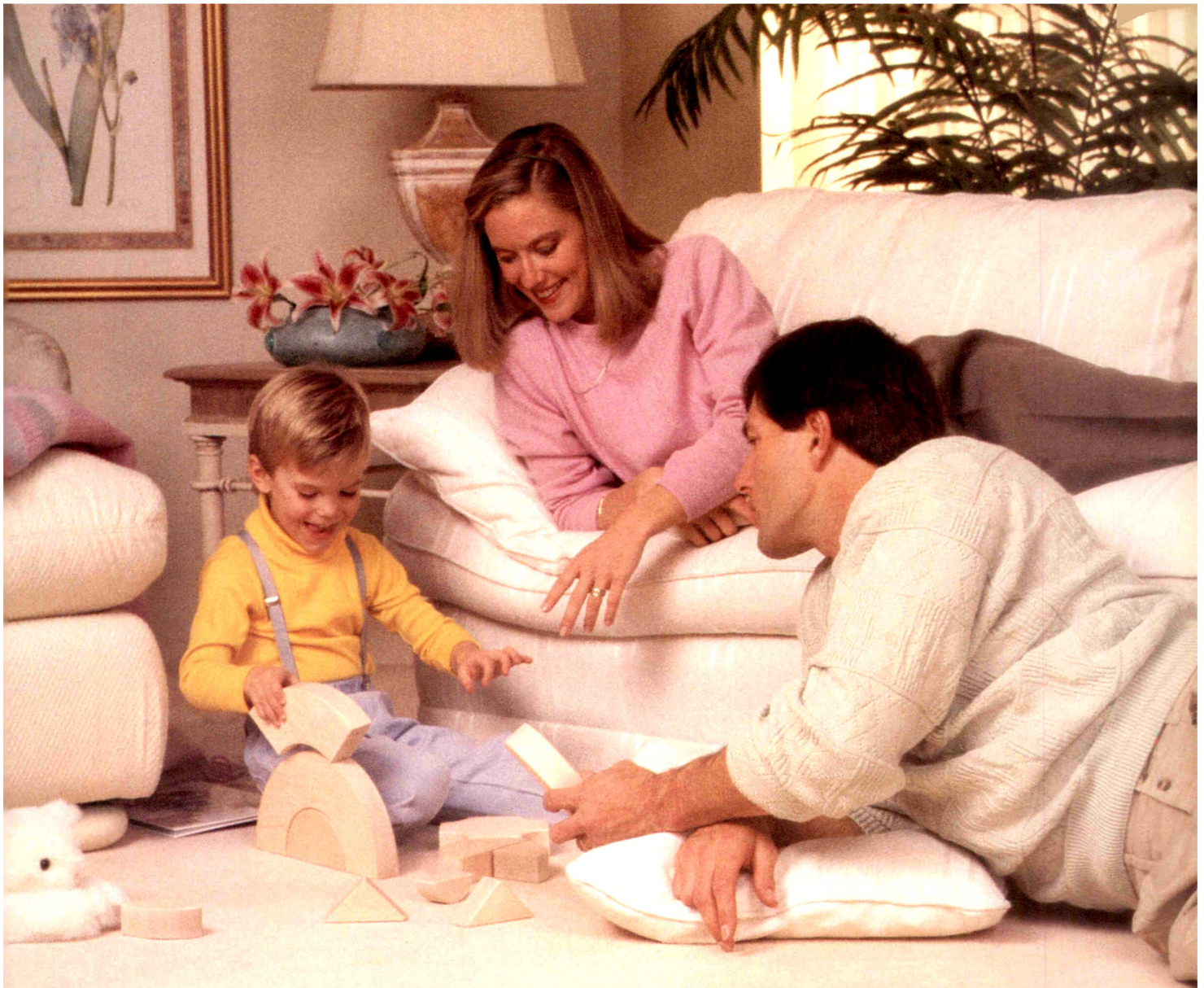
Dr. Whitelaw (Closing). Dr. Loring, I don't have an alternative to the court system. I firmly believe that there is a role for arbitration although I recognize that insurance companies don't like to hear this. In this study the one case that was arbitrated resulted in a defense verdict, but the plaintiff exercised her option to take it to court and the company paid her $7000 not to. Somehow we usually get to the issue of who has the best lawyer and who can do the best job of swaying the jury. I am not sure that I, anymore than anybody else, have an answer to that.

Dr. Russell, 11 of the 87 cases went to trial and nine of those resulted in a defense verdict. Medical review audit committees did play a role at one time, but usually the expectations for their effectiveness were not met. However, they did provide the defense attorneys with access to physicians with an unbiased view who are skilled in case review and at no cost to the company. For this article I used those reports that were available only for assessment of the standard of care. Your points on closed case review and the major problem of failure to diagnose are both very well taken.

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1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exits, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of the method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained elevated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI persisted for at least 9 years in women 40- to 49-years-old who had used OC's for 5 or more years. Findings in both studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polysystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with the use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind.

In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests.

As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, hemolytic uremic syndrome.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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The efficacy of external cephalic version and its impact on the breech experience

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With the introduction of ultrasonography, tocolysis, and electronic fetal monitoring, external cephalic version is considered safer and is more frequently used for the management of breech presentation. A retrospective review of a level III obstetric unit for the year 1988 is reported. Three hundred fifty-seven breech births were recorded. One hundred twelve patients were seen for external cephalic version. Forty-seven patients (48.9%) were successfully converted from breech. The cesarean section rate of successful versus unsuccessful version was 17.2% and 77.5%, respectively, which demonstrates the effectiveness of the technique. The overall impact is small. Success measured as a vaginal cephalic delivery of a previously known breech presentation represented <0.5% of all deliveries and <10% of all breech deliveries at this institution during 1988. (Am J Obstet Gynecol 1990;162:1459-64.)

Key words: External cephalic version, breech presentation, reducing cesarean section rates

Breech presentation has always been a challenge to those physicians who are involved with the birthing process. A historical study of obstetric care for breech presentation reveals the following: Hippocrates was said to practice external cephalic version, but when all attempts failed, fetal destruction was carried out and a large number of enabling instruments were designed over the ensuing centuries.[1] Mauriceau, Smellie, Veit, and Braxton Hicks were but a few who began to understand the mechanism of breech delivery and to develop techniques of assisting and extracting the breech.[2] Piper added forceps to the aftercoming head.[3] Some, such as Potter, became so enamored with breech delivery that all of his infants were delivered by breech extraction, even with internal version if necessary. During the twentieth century, cesarean section became safer for mothers and its liberal use has nearly eliminated the fetal mortality associated with breech presentation.[4]

Our ethical dilemmas through the years have progressed through maternal mortality, fetal mortality, fetal morbidity, and currently, cesarean section rates. The science and philosophy of the above tend to be interpreted within the egocentric framework of the "art" and the "technology" of obstetrics.

Beginning in the late 1960s, neonatal life support technology advanced so rapidly that in less than 20 years the age of viability decreased from 35 to 25 weeks' gestation. The survival of very-low-birth-weight infants in today's neonatal intensive care units has nearly eliminated the heartrending decision as to when appropriate and safe operative intervention of pregnancy is reasonable.

Because the incidence of breech presentation is inversely related to the gestational age at birth,[5] and since the overwhelming evidence supports cesarean section as the delivery method of choice for the premature breech, it would follow that the number of infants born from the breech may increase as the age of viability continues to decrease and the number of cesarean sections will correspondingly increase. The obstetric delivery method of choice for the term breech is not as clearly defined.[6-8] Cesarean section today has significantly reduced neonatal mortality. However, neonatal morbidity with cesarean section and vaginal delivery seemingly are the same.[6]

This article addresses the following questions: (1) is external cephalic version near term effective? (2) is it safe? and, (3) in a large obstetric service, does it have any impact on the overall breech experience and cesarean section rate?

Material and methods

A retrospective review of a level III obstetric service in a community teaching hospital was completed for the year 1988. Attention focused on all patients scheduled for external cephalic versions, and all those with breech presentations at the time of delivery.

Our protocol provides that any candidate for external cephalic version be admitted to the labor suite to ensure the availability of emergency services. After appropriate informed consent and permit signatures, fetal monitors are applied and ultrasonographic evaluation is done to determine presentation, placental localization, and amniotic fluid volume. Ultrasono-

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Table I. Scheduled outpatient appointments for external cephalic version

	Appointments	*Failed appointments*	*Appeared*	*Vertex on admission*	*Attempted version*
No.	148	36	112	16	96
Total (%)	100	24.3	75.7	10.8	64.9

Table II. Number and percent of successful and unsuccessful external cephalic versions

	Attempted	*Successful*	*Unsuccessful*
No.	96	47	49
Total (%)	100	48.9	51.0

graphically directed manipulation of the breech under tocolysis with either intramuscular or intravenous terbutaline is followed by electronic fetal monitoring. Rh immune globulin is administered when indicated. With adequate reassurance of fetal well-being, the patient is usually discharged to continue prenatal care at home and to await the onset of labor.

A successful version is defined as a conversion from breech to cephalic presentation. The ultimate outcome of pregnancy in both groups, successful version and unsuccessful version, is evaluated and compared. All breeches, corrected breeches, and the overall cesarean section rates for 1988 are then related to cephalic version.

One hundred forty-eight patient appointments for external cephalic versions were scheduled during the year 1988 (Table I). One hundred twelve visits were recorded. Thirty-six patients failed to keep their appointments. Ultrasonographic screening revealed an additional 16 patients whose fetal presentation was cephalic. External cephalic version was therefore attempted on 96 patients.

Results

Forty-seven (48.9%) successful versions from breech to cephalic presentation were accomplished (Table II). Forty-nine (51.0%) attempts were unsuccessful. Subsequent follow-up (Table III) revealed that 38 (80.8%) of the patients with successful versions were delivered vaginally. Eight patients (17.0%) were delivered by cesarean section and one was lost to follow-up. One fetus reconverted to a single footling breech and was delivered by cesarean section. The most common indication for cesarean section was failure to descend in labor.

Forty-nine attempts at cephalic version were unsuccessful. Examination of this group showed that 38 (77.5%) were eventually delivered by cesarean section, and five (10.2%) were delivered vaginally, (three breech, two cephalic). One of the cephalic presentations followed a repeat and successful version. One spontaneously converted to a cephalic presentation. Four patients of this group were lost to follow-up. The common indication for cesarean section of this group was breech presentation. Sixteen patients admitted for external version were found to have a cephalic presentation. Follow-up of this group showed that 10 women were delivered vaginally, four by cesarean section, and one was lost to follow-up. All vaginal deliveries were cephalic presentations. Two of the cesarean sections were for breech presentation. Thirty-five patients failed to keep appointments for external version. Follow-up of this group was nearly impossible. Pregnancy outcome could be determined in only seven of those 35 patients. Two were delivered vaginally and five had cesarean sections.

There was no recorded morbidity associated with the version procedure within the study. Maternal or fetal hemorrhage, fetal injury, fetal distress, premature labor, or premature rupture of membranes were not observed.

In 1988, 6627 births were recorded in the index institution (Table IV). There were 908 (13.7%) primary cesarean sections and 539 (8.1%) repeat cesarean sections [total, 1447 (21.8%)]. Three hundred fifty-seven (5.4%) of all infants were born from a breech presentation. Of all breech presentations (357), 73 (20.4%) were delivered vaginally, 284 (79.5%) were delivered by cesarean section (231 (64.7%) primary, and 53 (14.8%) repeat cesarean sections).

It is customary in the literature to correct breech presentation statistics for intrauterine death, twins, and congenital anomalies. Table V lists by weight-specific category all infants born from a breech presentation excluded according to these criteria. Table VI shows that 36 (13.6%) corrected breech infants were delivered vaginally. Two hundred twenty-eight (86.3%) were delivered by cesarean section. Therefore, excluding those breeches associated with intrauterine death, multiple gestation, and congenital anomalies, the corrected number of breech deliveries was 264. Excluding prematurity, and thereby focusing on single healthy infants with birth weights greater than 2500 gm, there was a total of 150 term healthy breech infants. One hundred thirty-four (89.3%) of these were delivered by cesarean section and 16 (10.7%) were delivered vaginally.

In summary, of 6627 recorded births during 1988, 1447 (21.8%) were delivered by cesarean section. After

Table III. Mode of delivery and presentation at birth of those patients scheduled for external cephalic version

		Vaginal delivery		*Cesarean section*		*Presentation at birth*		
	No.	*No.*	*%*	*No.*	*%*	*Vertex*	*Breech*	*Unknown*
Successful version	47	38	80.8	8	17.0	45	1	1
Unsuccessful version	49*	5	10.2	38	77.5	2	41	4
Vertex on admission	16	10	62.5	5	31.2	13	2	1
No shows	36	2		5		2	5	28

*Includes two repeat attempts at version.

Table IV. Comparison of delivery for all births and breech presentations for 1988

	Number	*Vaginal*	*Primary cesarean section*	*Repeat cesarean section*	*Total cesarean section*
All presentations	6627	5180	908	539	1447
	(100)	(78.2)	(13.7)	(8.1)	(21.8)
Breech presentations	357	73	231	53	284
	(5.4)	(1.1)	(3.5)	(0.8)	(4.3)
	[100]	[20.4]	[64.7]	[14.8]	[79.5]

Numbers in parentheses represent the percentage of all presentations; numbers in brackets represent the percentage of all breech presentations.

correction for prematurity, fetal death, multiple gestation, and congenital anomalies, 150 term infants were delivered from the breech presentation. One hundred thirty-four (89.3%) were delivered by cesarean section. Sixteen (10.7%) were delivered vaginally. In addition to the above breech presentations, 47 successful cephalic versions were accomplished. If it is assumed that the cesarean section rate for these cases is 89.3%, if the infants had remained in the breech presentation, an additional 41 cesarean sections would have been required to deliver all breech cases for the year 1988. The overall cesarean section number would rise from 1447 (21.8%) to 1488 (22.4%), a difference of 0.6%.

Comment

The management of breech presentation and delivery in the United States has encompassed scientific, legal, and ethical consideration of both mothers and infants. Within the lifetimes of many of us, maternal risk from cesarean section has been dramatically reduced.

It is my opinion that too many of our recently trained specialists consider cesarean section a safer and better method of breech delivery for both mother and baby than use of forceps, or any manual manipulation of the fetus. Without exception, no other obstetric variation but the breech presentation has provided us the opportunity to abandon all scientific information, and to plunge forthwith into operative intervention. This is substantiated in this review by the following observations. Almost 90% of all term breech presentations were delivered by cesarean section, and there was an alarming lack of documentation concerning the classification of the breech presentation. The predominant indication for operative intervention was "breech in labor."

Table V. Number of breech infants by weight-specific categories excluded for intrauterine death, twins, and congenital anomalies

	Birth weight			
Delivery method	*0-750 gm*	*750-1500 gm*	*1500-2500 gm*	*>2500 gm*
Vaginal delivery				
Intrauterine fetal death	8	6	2	0
Twins	4	2	7	6
Congenital anomalies	0	2	0	0
Subtotal	12	10	9	6
Primary cesarean section				
Intrauterine fetal death	0	0	0	0
Twins	3	7	21	10
Congenital anomalies	0	0	1	4
Subtotal	3	7	22	14
Repeat cesarean sections				
Intrauterine fetal death	0	0	0	0
Twins	0	0	7	3
Congenital anomalies	0	0	0	0
Subtotal	0	0	7	3
TOTAL	15	17	38	23

There has been a significant effort both in the profes-

Table VI. Uncorrected and corrected breech presentations by weight-specific categories and mode of delivery

Mode of delivery	Total		Birth weight			
	No.	%	0-750 gm	750-1500 gm	1500-2500 gm	>2500 gm
Vaginal	73	20.4	22	11	18	22
	(36)	(13.6)	(10)	(1)	(9)	(16)
Primary cesarean section	231	64.7	8	31	73	119
	(185)	(70.1)	(5)	(24)	(51)	(105)
Repeat cesarean section	53	14.8	1	8	12	32
	(43)	(16.2)	(1)	(8)	(5)	(29)
All cesarean sections	284	79.5	9	39	85	151
	(228)	(86.3)	(6)	(32)	(56)	(134)
TOTAL	357	100	31; 8.7%	50; 14.0%	103; 28.8%	173; 48.5%
	(264)	(100)	(16)(6.1%)	(33)(12.5%)	(65)(24.6%)	(150)(56.1%)

Numbers in parentheses are corrected.

sional and lay literature to resurrect the technique of external cephalic version as a means of reducing our increasing and alarming cesarean section rate. Resurrection of the technique itself is not new. In another age, according to Edgar in 1904,[1] "Before the sixteenth century, it (cephalic version) was practically the only version used, but at that time podalic version was introduced and because of the ease of its performance, became very popular, and on this account, cephalic version was almost abandoned, although more recently revived by some obstetricians." External cephalic version became a well-recognized procedure after the publication of Hubert and Pinard in the 1800s,[2] it was found to produce a zero neonatal mortality by Mehta in 1944,[4] was advocated by Macarther in 1964,[9] and was said to have decreasing value by Bradley-Watson in 1975.[10] Ylikorkala and Hartikainen-Sorri[11] first reported the use of ultrasonography in conjunction with external version, and finally tocolysis became a factor that was to further reduce the complications and increase the success of cephalic version.[12-14]

In this review, I was surprised, as were Flanagan et al. in their presentation to this society in 1987,[15] to discover that our current success for external cephalic version was <50%. This success rate, despite ultrasonography and tocolysis, is little different than that reported by both Williams[2] and Edgar[1] at the turn of the century. However, the overwhelming difference in the rate of cesarean section versus vaginal delivery among successful versus unsuccessful versions is striking. The study demonstrates that in a community-based level III teaching obstetric service, 38 women who underwent cephalic version near term were delivered vaginally, thereby avoiding maternal risk, cost, and neonatal morbidity associated with cesarean section for breech presentation.

The technique of version is apparently safe. At no time in the 96 attempted external versions was a major maternal or fetal complication recorded.

Finally, is there a major impact on the 1988 cesarean section rate by the use of external cephalic versions? Routine cesarean section for breech presentation was initially recommended in 1959[7] and became common in the United States in the mid-1970s, presumably as the legal risk of vaginal delivery of a breech presentation increased. This review demonstrated an almost 90% cesarean section rate for corrected term breech delivery. With this approach to the treatment of the breech, any attempt to prevent a breech presentation is valuable. Successful cephalic version allowed 38 women to be delivered vaginally and thereby avoid cesarean section. On a service where 6664 obstetric deliveries were recorded, 1447 cesarean sections were performed. Sixteen singleton term breeches were permitted to be delivered vaginally. External cephalic version reduced the potential cesarean section rate by 0.6%. The resurrection of an ancient technique for a far different reason than during the days of Hippocrates remains valid. To consider cephalic version a solution to our current problem of high cesarean section rates is not substantiated and we must seek other studies to determine methods that might significantly lower the cesarean section rate in the United States.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. DAVID PENT, Phoenix, Arizona. There has been considerable interest, both within our profession and in the media, concerning the high cesarean section rate and how to lower it. Dr. Brooks Ranney, in his 1973 paper, "The Gentle Art of External Cephalic Version," which detailed his experience with 860 attempted cephalic versions, stated that "conservatively estimated in various ways, the probable cesarean section rate for this entire group, without the use of version, would have been between 9% and 10%," instead of the 7.2% rate he reported.[1] As recently as last year, the "Update" audio cassette tapes,[2] sponsored by the American College of Obstetricians and Gynecologists, in an issue on cesarean sections, noted that the rate could be reduced by an increase in vaginal births after cesarean section and by the more widespread use of external cephalic version.

Dr. Hanss' paper beautifully illustrates that in his hospital the impact of external version on the section rate is disappointingly small. Even his figures, I believe, are optimistic. Very simply, we do not know how many of the fetuses who were successfully turned by external version would have turned spontaneously before the onset of labor. The patients in this series were at 36 weeks or later in gestation. Dr. Raymond Jennett graciously provided me a computer printout of his statistics from St. Joseph's Hospital in Phoenix. At 36 weeks' gestation 8.168% of the deliveries were breech, and at 40 weeks' this figure was 4.403%. This represents a spontaneous 46% change, remarkably similar to Dr. Hanss' reported 49% successful version rate. Obviously there are errors inherent in the comparison, including the fact that some of the version patients were past the thirty-sixth week, and also that the percentage of breeches delivered at any gestational age is greater than the percentage of fetuses in the breech position, since the latter position is thought to be conducive to premature labor. Similarly, it is unfortunate that more data could not be obtained regarding the patients who failed to keep their appointments for external version. Of the seven patients for whom we have data, two converted spontaneously. That represents 29%, but of course the numbers are too small for statistical significance.

Brooks Ranney notes that attitudes concerning external cephalic version may be summarized by quoting J. L. Macarthur, who wrote, "There are those who enthusiastically recommend it, others who violently oppose it and still others who express a rather elegant distaste for it."[3] Indeed as one reviews the literature, one sees dogmatic statements made both for and against version, with an extreme paucity of any type of data to support the conclusions. What is needed, now that we have entered the era of ultrasonography, fetal monitoring, and tocolysis, is data to relate how many fetuses are breech presentations at any given time in gestation and what is their "natural history." This could be ascertained by ultrasonographic examination, which would be able to define the exact presentation, because it is thought that frank breeches are more difficult to turn, with the extended legs acting as splints. Therefore there may be value in identifying a subgroup of breech presentation for whom version may or may not be of value. It also would be profitable to compare hospitals, or groups of physicians, who do versions with those who do not. This has been reported in the past, and claims were made that hospitals that do not do versions had lower morbidity and mortality rates, but the exact figures are hard to determine and do not reflect the techniques currently being used.

Finally, we need more data to evaluate cost effectiveness. At Dr. Hanss' hospital, the hospital charge for a vaginal delivery ranges from $1800 to $2600. The hospital charge for an external cephalic version is $900, one third to one half the cost of a vaginal delivery. At that price we will have difficulty teaching versions to residents, so that they can develop the important necessary experience.

I have two questions for Dr. Hanss. First, he mentions one unsuccessful version that was converted on a second attempt. Were there any other patients who underwent more than one attempt at cephalic version? Dr. Ranney probably holds the record in this regard, finally turning a baby on his eighth attempt and raising the question as to who was more stubborn—the fetus or the physician. Second, what were the contraindications for external cephalic version in these cases?

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DR. HANSS (Closing). Dr. Pent, there were only two repeat versions attempted. There is no effort on our

service to select patients based on the volume of amniotic fluid nor on the type of breech. All women who were seen with breech presentations were accepted for an attempt at version. Perhaps that lack of selection lowered the percentage of success. The earlier that version is attempted—at 28, 30, or 32 weeks—the greater the success rate. Not only are there more breech cases at 30 weeks, but at this gestational age the majority would spontaneously convert to cephalic presentation. The only contraindications to version in this study were ruptured membranes or loss of heart rate variability on the monitor.

Green et al.[1] pointed out in 1982 that the perinatal morbidity associated with vaginal delivery of a breech presentation is similar to that with cesarean section. In my review, I found a number of breech infants born by cesarean section who had low Apgar scores. I did not count them so I do not have a definite answer. We can certainly eliminate the destructive instruments that obstetricians have known in the past, but we still must teach our residents the mechanism of breech delivery and some techniques for breech delivery including the Mauriceau-Smellie-Veit, the modified Prague maneuver, and the use of Piper forceps. Delivering a breech infant through an abdominal wall incision is very little different in terms of the mechanisms from delivering a breech through the vaginal canal. Today, many of our residents are deficient in the knowledge and skill necessary to safely extract a breech from the uterus, even through a lower uterine incision.

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Diagnostic and therapeutic curettage in gestational trophoblastic disease

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From June 1976 through June 1989, 37 nonconsecutive patients underwent uterine curettage during the course of their gestational trophoblastic disease. In 22 patients (59%) trophoblastic tissue was obtained. Three (8.1%) patients sustained a uterine perforation during the procedure. In six patients curettage was performed for bleeding. There were six patients curetted during assessment for metastatic trophoblastic disease. Twenty-eight patients underwent curettage for the presumed diagnosis of nonmetastatic gestational trophoblastic disease. In retrospect, four of these women (14.3%) had insufficient criteria for the diagnosis of gestational trophoblastic disease. Of the remaining 23 patients, four (17.4%) went into clinical remission without further treatment. Ten patients (43.5%) had a transitory decline in serum β-human chorionic gonadotropin levels that subsequently rose or plateaued. Six patients (26.1%) showed no effect from the curettage on their serum β-human chorionic gonadotropin trend during a short period of observation. Three patients (13.0%) with nonmetastatic gestational trophoblastic disease were not observed for a possible therapeutic effect after curettage. Thus, in only 4/20 (20%) women with nonmetastatic trophoblastic disease was a therapeutic effect from curettage shown. (AM J OBSTET GYNECOL 1990;162:1465-71.)

Key words: Curettage, gestational trophoblastic disease, effectiveness, risks

Uterine curettage has traditionally been regarded as important for diagnostic and therapeutic reasons in the assessment of women with gestational trophoblastic disease.[1-3] In fact repeated curettages have been a common practice.[4] Yet there has been little critical evaluation of curettage in this setting.[4-6] For this reason a retrospective review of the uterine curettages performed in women presumed to have gestational trophoblastic disease at our institution was undertaken. The purpose of this study is to examine the advantages and disadvantages of curettage in women with gestational trophoblastic disease.

Material and methods

The medical records of all patients who underwent uterine curettage during follow-up for hydatidiform mole or suspected gestational trophoblastic disease at Los Angeles County–University of Southern California Women's Hospital were reviewed. Twenty women were curetted during the 46-month period from June 1976 through March 1980. Two of these women had a gestational choriocarcinoma not preceded by a hydatidiform mole. Interest in curettage for such patients waned during the next 7 years. Another 17 women underwent curettage during follow-up for hydatidiform mole in the 20-month period from November 1987 through June 1989. During these two time periods a repeat curettage was performed during the follow-up for hydatidiform mole if (1) β-human chorionic gonadotropin serum (β-hCG) levels plateaued or rose or (2) excessive uterine bleeding occurred.

The clinical records were reviewed for initial management of the hydatidiform mole, the presence of bleeding, the size of the uterus, the trend of serum β-hCG levels before the curettage, the level of serum β-

Table I. Uterine curettage results and serum β-hCG levels in patients with nonmetastatic trophoblastic disease

Curettage specimen	*No. of patients*	*Serum β-hCG (mIU/ml)*	
		Mean	*Range*
Gestational trophoblastic disease	6	11,292	1,220-16,362
Trophoblastic cells	6	4,716.5	259-15,947
Chorionic villi	3	2,396.7	140-4,500
Normal endometrial tissue	9	7,019.3	14-20,900

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6/6/20739

Table II. Uterine curettage performed for excessive bleeding from gestational trophoblastic disease

Patient	Serum β-hCG		Uterine size	Pathologic histology		Days after mole-pregnancy	Outcome	Other
	mIU/ml	Trend curettage		Gm	Tissue			
P. C.	1080	Falling	Normal†	18	Atypical trophoblasts	32	Lost to follow-up	Blood transfusion
D. D.	6200	Falling	Large‡	200	Decidua, blood	31	Spontaneous remission	
M. H.	1800	None*	Large	30	Hydatidiform mole	16	Spontaneous remission	
L. M.	77800	None*	Large	230	Hydatidiform mole	7	Spontaneous remission	
A. P.	278	Falling	Normal	3	Endometrium	31	Chemotherapy; remission	Lung metastasis
P. F.	3880	None*	Normal	9	Choriocarinoma	197	Chemotherapy; hysterectomy; remission	Perforation

*Single value (?).
†<8 Weeks' gestational size.
‡>8 Weeks' gestational size.

Table III. Uterine curettage performed in patients with metastatic trophoblastic disease

Patient	Serum β-hCG		Uterine size	Pathologic histology		Days after mole-pregnancy
	mIU/ml	Trend at curettage		Gm	Tissue	
L. G.	870	Plateau	Normal*	Fragments	Endometrium	48
J. M.	665	Plateau	Normal	18	Endometrium	40
A. P.	278	Declining	Normal	3	Endometrium	31
S. S.	1070	Plateau	Normal	2	Hydatidiform mole	59
G. A.	86400	None	Large†	7	Endometrium	79
M. L.	550	Plateau	Normal	2	Decidua	41

*<8 Weeks' gestational size.
†>8 Weeks' gestational size.

hCG at the curettage, and for evidence of metastasis. Further, the quantity of the curettage specimen and the histologic descriptions were analyzed.

A uterus was considered enlarged if a sounding exceded 10 cm or the estimate of size was >8 weeks' gestational size. Persistent gestational trophoblastic disease was diagnosed by a rise or plateau in serum β-hCG levels or by the appearance of metastasis. A rising trend in serum β-hCG levels was defined as doubling in value over a 2-week period. A plateau in hCG levels was generally considered to be present when no decrease in serum β-hCG level was apparent during 3 weeks of observation and any increase was insufficient to qualify as a rising trend. Assessment for metastasis included history and physical examination, liver function tests, chest roentgenogram, pelvic ultrasonographic examination, and computerized tomography of the chest, abdomen, brain and pelvis. Earlier patients underwent radioisotope scans of the brain and liver and pelvic angiography. The uterine curettage specimen was considered positive if a histologic diagnosis of a gestational trophoblastic disease or trophoblastic cells were detected, otherwise it was considered negative for diagnostic purposes.

Last, the details in management and clinical outcome were determined for all patients.

Results

General observations. The yield from the curettages were analyzed for the 24 women with nonmetastatic

Table IV. Uterine curettage in patients with unsubstantiated trophoblastic disease in retrospect (immediate precurettage titer hCG showed decline*)

Patient	Serum β-hCG		Uterine size	Pathologic histology		Days after mole-pregnancy	Outcome
	mIU/ml	Trend at curettage		Gm	Tissue		
E. C.	1400	Plateau	Large†	5	Trophoblastic	45	Hysterectomy for perforation, remission
P. C.	1080	Plateau	Normal‡	18	Atypical trophoblastic	32	Lost to follow-up
R. F.	133	Plateau	Normal	3	Chorionic villi	76	Spontaneous remission
K. B.	1640	Rise	Normal	1	Endometrium	49	Spontaneous remission

*Value not received until after curettage.
†>8 Weeks' gestational size.
‡<8 Weeks' gestational size.

Table V. Uterine curettage followed by spontaneous remission of nonmetastatic trophoblastic disease

Patient	Serum β-hCG		Uterine size	Pathologic histology		Days after mole-pregnancy	Outcome
	mIU/ml	Trend at curettage		Gm	Tissue		
R. M.	643	Rise	Normal*	1	Trophoblasts	53	Spontaneous remission in 20 days
B. C.	25200	Plateau	Large†	16	Hydatidiform mole	62	Spontaneous remission in 30 days
V. M.	5430	Rise	Normal	2	Bizarre trophoblasts	42	Spontaneous remission in 42 days
R. D.	259	Plateau	Normal	8	Trophoblasts	88	Spontaneous remission in 11 days

*<8 Weeks' gestational size.
†>8 Weeks' gestational size.

trophoblastic disease (Table I). Fifteen of 24 (62.5%) of those patients exhibited some aspect of trophoblastic histology.

The uterine sizes were analyzed in reference to the diagnostic yield on the curettages. The curettings from eight of 12 (66.7%) large uteri contained trophoblastic elements. The curettings from 25 normal-sized uteri showed trophoblastic tissue in 13 (52%).

Bleeding. Six patients underwent uterine curettage because of significant bleeding (Table II). Four of these women were clinically considered to have retention of molar tissue after evacuation. Two of these patients were evacuated at our institution, one (P. C.) by suction and sharp curettage to complete spontaneous abortion of the hydatidiform mole and the other (L. M.) underwent elective suction and sharp curettage for an intact hydatidiform mole. No details of primary management are known for the other two women (M. H., D. D.). One woman with metastatic postmolar trophoblastic disease and one woman with postabortal choriocarcinoma also underwent curettage. It should be noted that this last patient sustained a uterine perforation that led to laparotomy and hysterectomy.

Persistent trophoblastic disease

Metastatic. Six patients underwent uterine curettage as part of their assessment for metastatic trophoblastic disease (Table III). The preceding gestation in five patients was a hydatidiform mole and a tubal pregnancy in one (G. A.). One patient (A. P.) with metastasis was first seen with bleeding and is included under both groups of patients.

Nonmetastatic. A total of 28 women underwent uterine curettage for presumed nonmetastatic postmolar trophoblastic disease on the basis of the trend of serum hCG levels. Two women with serum hCG trends suggesting postmolar trophoblastic disease also were first seen with bleeding and are included in Table II.

Despite a trend of serum β-hCG levels to substantiate the diagnosis of nonmetastatic postmolar trophoblastic disease, four patients had a significant drop in β-hCG level in the serum specimen drawn immediately before curettage (Table IV). Therefore, in retrospect the di-

Table VI. Uterine curettage followed by a nonsustained fall in serum β-hCG levels in patients with nonmetastatic trophoblastic disease

	Serum β-hCG			*Pathologic histology*			*Serum β-hCG (mIU/ml)*		
Patient	*mIU/ml*	*Trend at curettage*	*Uterine size*	*Gm*	*Tissue*	*Day after mole-pregnancy*	*At nadir*	*At start of treatment*	*Trend*
S. W.	140	Plateau	Normal*	5	Chorionic villi	32	18	37	Plateau
T. C.	1170	Rise	Normal	3	Necrotic trophoblasts	29	273	648	Rise
M. M.	5340	Plateau	Large†	15	Hydatidiform mole	29	520	645	Plateau
H. S.	16362	Rise	Large	225	Hydatidiform mole	26	2130	7100	Rise
T. D.	15700	Rise	Normal	3	Hydatidiform mole	39	378	915	Rise
S. J.	3380	Plateau	Normal	24	Trophoblasts	42	638	1190	Plateau
A. A.	20900	Plateau	Normal	1	Endometrium	57	8933	11900	Plateau
V. M.	2550	Rise	Normal	2	Chorionic villi	37	2300	6900	Plateau
E. S.	1270	Plateau	Normal	4	Hydatidiform mole	34	834	930	Plateau
L. R.	15947	Plateau	Large	730	Trophoblasts	26	15100	16600	Plateau

*<8 Weeks' gestational size.
†>8 Weeks' gestational size.

Table VII. Uterine curettage without effect in patients with nonmetastatic trophoblastic disease

	Serum β-hCG			*Pathologic histology*			*Serum β-hCG (mIU/ml)*	
Patient	*mIU/ml*	*Trend at curettage*	*Uterine size*	*Gm*	*Tissue*	*Days after mole-pregnancy*	*At treatment*	*Trend*
J. W.	14	Plateau	Normal*	3	Endometrium	152	17	Plateau
L. M.	6140	Plateau	Normal	2	Necrotic cellular debris	31	7300	Plateau
B. A.	2920	Rise	Normal	2	Blood	30	4310	Plateau
T. M.	5700	Rise	Large†	1	Blood	47	16000	Rise
N. V.	2640	Plateau	Large	6	Trophoblasts	43	6820	Rise
C. M.	4030	Rise	Normal	4	Endometrium	36	13100	Rise

*<8 Weeks' gestational size.
†>8 Weeks' gestational size.

agnosis of postmolar trophoblastic disease at the curettage could not be sustained. The diagnostic and therapeutic effects of these curettages are also questionable. However, one patient (E. C.) did have an invasive mole. Another patient (P. C.) is also included among those curetted for bleeding in Table I.

After curettage four patients went into complete remission without further treatment. There was no clinical suspicion noted that incomplete evacuation of the hydatidiform mole had occurred in these patients (Table V).

Ten patients had a decline in serum β-hCG values after curettage that was not sustained (Table VI). All these women subsequently had a serum β-hCG trend again indicating postmolar trophoblastic disease. All were successfully treated to remission with chemotherapy.

Six patients underwent curettage at the time of diagnosis of nonmetastatic gestational trophoblastic disease and showed no effect from this procedure on their disease as evidenced by a continuous plateau or rise in serum β-hCG levels during a period of observation afterward (Table VII). All these women were treated to successful remission with chemotherapy.

Four women with nonmetastatic trophoblastic disease had no postcurettage follow-up, which rendered them unevaluable for therapeutic effect from this procedure (Table VIII). One patient (P. F.) included here was also considered among the patients who were first seen with bleeding (Table II).

Comment

The curettages done for bleeding were not elective procedures and, as mentioned previously, four of these clinical situations were considered incomplete molar evacuations. But the presence of bleeding, the declining trend in serum β-hCG levels, molar tissue in 2/4 patients, and spontaneous remission after curettage fit

Table VIII. Uterine curettage without follow-up in patients with nonmetastatic trophoblastic disease

Patient	Serum β-hCG		Uterine size	Pathologic histology		Days after mole-pregnancy	Outcome
	mIU/ml	Trend at curettage		Gm	Tissue		
A. G.	4500	Rise	Large	350	Blood, endometrium	36	Chemotherapy, remission
M. S.	4500	Plateau	Normal	2	Trophoblasts	28	Chemotherapy, remission
T. G.	17800	Rise	Normal	0	Endometrium	27	Perforation, laparotomy, lost to follow-up
P. F.	3880	None	Normal	9	Choriocarcinoma	197	Perforation, hysterectomy, chemotherapy, remission

Table IX. Therapeutic effect of curettage in nonmestatic trophoblastic disease

	No.	Serum β-hCG (mIU/ml)		Positive curettage	
		Mean	Range	No.	%
Remission with curettage	4	7883	259-25200	4/4	100
No remission with curettage	16	6513	14-20900	9/16	56.25

well with the concept of incomplete abortion as opposed to nonmetastatic postmolar trophoblastic disease. Two of these women had their initial evacuation at our institution. During the time periods of this study 140 patients received initial management of their molar pregnancy at Women's Hospital for a 2/140 (1.4%) incomplete evacuation rate.

In this series 21 of 37 women (56.8%) had curettages that revealed trophoblastic tissue. This experience is similar to the 46% and the 70% positive curettage rate reported in the two series by Berkowitz.[5, 6] Only nine (24.3%) women had a sufficient curettage specimen to allow a histologic diagnosis (eight hydatidiform moles and one choriocarcinoma). Nine women (24.3%) had trophoblastic tissue that, although insufficient in amount for histologic diagnosis would still allow analysis for prognostic features such as those described by Hertig[7] and Deligdisch.[8] Inasmuch as all patients who were not lost to follow-up in this series had remission of their disease with curettage, chemotherapy, hysterectomy, or a combination of these modalities, it is difficult to make a statement with regard to the importance of histologic diagnosis in clinical management.

Berkowitz[5] found that one course of chemotherapy with methotrexate and citrovorum factor was definitive therapy for 95% of trophoblastic disease patients who had no trophoblastic tissue in the curettage specimen, whereas 59% of women with trophoblastic tissue in their curettages required more than one course of therapy for clinical remission. It has been the practice at our institution to treat such women with weekly or biweekly courses of chemotherapy until one course has been given after a normal serum β-hCG level. This practice and the fact that several different chemotherapy regimens have been used in these women does not allow comparison on this point with the Berkowitz[5] series.

With the use of a serum β-hCG level of 50,000 mIU/ml Berkowitz[5] found a rough correlation with trophoblastic tissue in the curettage specimen and multiple courses of chemotherapy. However, in this present series (Table I) there was no apparent correlation between trophoblastic tissue in the curettings and serum β-hCG levels in patients with nonmetastatic trophoblastic disease. Therefore as a predictor of response, serum β-hCG levels seem more applicable clinically than diagnostic curettage results.

In our small experience with uterine curettage in metastatic gestational trophoblastic disease no benefit of curettage on an elective basis could be shown.

It is likely that the tradition for repeated curettages is based on older experiences with patients, such as those in Table V, in whom a convincing therapeutic effect was apparent after a plateau or rise in serum β-hCG levels. The analysis in this report did not disclose how these four patients differed from those patients whose nonmetastatic trophoblastic disease persisted after curettage (Table IX) other than that all their cu-

rettages were positive for trophoblastic tissue versus a 9/16 (56.25%) positive rate for the others. It is probable that most or all their trophoblastic disease was located in the superficial myometrium and the endometrium, both within reach of the curette.[1] In this regard diagnostic imaging techniques could prove helpful in the selection of optimal candidates for therapeutic curettage. Berkowitz[5] has reported that ultrasonography can be helpful in the prediction of a positive curettage 73.9% (17/23) of the time.

The intriguing observation that curettage may be definitive therapy in 20% (4/20) of patients with nonmetastatic trophoblastic disease must be tempered by the fact that all three patients (8.1%) who sustained a uterine perforation required laparotomy and two underwent hysterectomy. These three curettages were performed by third-year resident physicians with staff physicians in attendance. It is well documented that myometrial invasion, perforation, and hemoperitoneum can all occur spontaneously with trophoblastic tumors. This process renders elective curettage for postmolar gestational trophoblastic disease a procedure with some risk to fertility. This is of particular concern because most of these women are young with a current interest in having children.

In view of these facts, unless a group to benefit therapeutically from curettage can be clearly identified, there does not appear to be a significant place for elective curettage in women with postmolar gestational trophoblastic disease.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Michael R. Smith, Seattle, Washington. Drs. Schlaerth and Morrow have reviewed for us the Los Angeles County Hospital experience with pretreatment curettage in the management of gestational trophoblastic neoplasia over the past 13 years. The purpose of their review was to assess the value of this traditional modality.

The data base consists of 37 patient records that detail curettage procedures in the course of gestational trophoblastic neoplasia evaluation. Six were done for bleeding, six for evaluation of metastatic disease, and 27 for assessment of nonmetastatic disease. Of the six done for bleeding, four were because of clinically obvious retained products after molar evacuation. In each case, bleeding was controlled and spontaneous remission ensued. In the fifth case, bleeding was controlled, but metastatic disease prompted chemotherapy. In the sixth case, uterine perforation prompted hysterectomy before chemotherapy.

No benefit, therapeutic or prognostic, was achieved in the five instances in which curettage was performed as part of the workup of metastatic gestational trophoblastic neoplasia.

Four of 27 who underwent curettage during evaluation of nonmetastatic gestational trophoblastic neoplasia required no further treatment. No therapeutic or prognostic benefit was noted in the remaining 23, and one required hysterectomy for uterine perforation.

Nine of 37 (24.3%) benefitted either through control of bleeding or eradication of disease. Two of 37 (5.4%) required hysterectomy for control of bleeding associated with postcurettage uterine perforation. Twenty-six of 37 (70.3%) derived no benefit whatsoever. All were ultimately cured of their disease.

The authors conclude that there is no clear indication for uterine curettage in the management of postmolar gestational trophoblastic neoplasia, except in the bleeding patient with evidence of retained tumor.

One must reconcile this advice with the recommendations of our colleagues in gynecologic pathology who, although not always in agreement with one another with regard to interpretation of an individual case, do find that the morphologic criteria found in the 60% or so of positive curettage specimens provide useful prognostic information.

Similarly, one must reconcile this advice with the recommendations of experienced clinicians who find that debulking of nonmetastatic gestational trophoblastic neoplasia by curettage may eliminate the need for chemotherapy in some patients and reduce the total number of treatment courses in others.

We are aided in our reconciliation by the abundance of data worldwide that show that the extraordinary specificity and sensitivity of the radioimmunoassay for the β-hCG far exceeds that of microscopic histopathology, immunochemistry, and diagnostic imaging in establishing both the diagnosis of gestational tropho-

blastic neoplasia and its response to treatment at no patient risk.

It is similarly abundantly clear that the success of systemic chemotherapy guided by serial β-hCG levels far exceeds that of surgical extirpation alone with comparable, or perhaps less, patient risk. Chemotherapy is clearly the gold standard, with surgery assuming an adjuvant role for resection of chemotherapy-resistent metastases or for elective hysterectomy in the patient with no interest in subsequent fertility.

The day before I received this manuscript, as if on cue a young woman 5 months after evacuation of a mole was referred to me. She had undergone two postevacuation curettage procedures before referral because of plateauing and subsequent elevation of her β-hCG titers even though her initial evacuation was thought to be complete and the first curettage was negative. She has since responded completely to three courses of methotrexate—two given while her titer was elevated and the final given after her titer returned to normal.

In 1981, Drs. Schlaerth and Morrow[1] helped us better understand the β-hCG regression curve, and today it is the role of uterine curettage in this disease. I look forward to their continued contribution to our understanding of this disease.

I have but one question for Dr. Schlaerth. If confronted with heavy bleeding in a young patient with postmolar gestational trophoblastic neoplasia and a normal sonogram or magnetic resonance imaging (MRI), how would you proceed?

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Dr. Hisham K. Tamimi, Seattle, Washington. We have used intraoperative ultrasonography after the evacuation of 20 molar pregnancies in the past 5 years. The only patient who required chemotherapy was one with lung metastasis. I welcome your comments about the potential for this technique to minimize the need of repeat curettage and even to reduce the need for chemotherapy.

Dr. Joseph Oliver, Pasadena, California. When do you allow these patients to become pregnant again? Did amenorrhea or Asherman's syndrome develop in any of your patients because of curettage?

Dr. Schlaerth (Closing). Dr. Smith asked what I would do about a patient with heavy bleeding from postmolar gestational trophoblastic disease if she had a sonogram and MRI that revealed nothing suspicious. In one such patient, we did a curettage and the sonogram turned out to be a false-negative one, as it is in this setting from time to time. I have little information about the MRI in this setting. It takes a rather long time to do an MRI, and heavy bleeding may not allow that. The bottom line here is that the clinical situation would dictate what I would do. With heavy bleeding, my first response would be curettage.

Dr. Tamimi, your question about intraoperative ultrasonography is part of a larger question of the role played by imaging and endoscopy in the identification of patients who might be cured with curettage alone. We continue to search for solutions to the dilemmas our study has shown and imaging techniques may be the answer.

Dr. Oliver, by and large, for patients with nonmetastatic disease, we ask for a 1-year interval before they become pregnant again. I am not aware of any of our patients in whom Asherman's syndrome developed subsequent to curettage. However, our long-term follow-up, as I am sure you realize, is poor.

Prenatal diagnosis of intracerebellar hemorrhage: Case report

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Evidence continues to accumulate that neurologic damage can occur during the antenatal period, unrelated to intrapartum events. We report a case in which intracerebellar hemorrhage was diagnosed by antepartum ultrasonographic examination. Correlation of fetal heart rate patterns, Apgar scores with neonatal course, and neuropathologic findings are presented. Medicolegal implications are discussed. (Am J Obstet Gynecol 1990;162:1472-5.)

Key words: Intracranial hemorrhage, intracerebellar hemorrhage, medicolegal implications

The availability of increasingly sophisticated imaging techniques has made it possible to diagnose hemorrhage and other intracranial lesions in the live infant before birth. This not only helps to support clinical decisions but allows comparison of fetal heart rate patterns, blood gas values, Apgar scores, and neonatal course with documented incidents of perinatal asphyxia in otherwise normal infants before an asphyxial event.

Case report

A 33-year-old woman was referred to the outpatient clinic at 35 weeks' gestation. The referring physician reported that the only unusual event before that time had been a hospital admission for suspected premature labor associated with a mild urinary tract infection. The patient had smoked more than a package of cigarettes a day throughout the pregnancy. No history of drug usage was obtained. Pertinent family history included her father and brother. Her father had incurred a stroke at age 32 followed by 7 years of coma before death. Her brother had a nonfatal myocardial infarction in his early 30s.

Two days after her initial clinic visit she reported a decrease in fetal movement. A nonstress test performed later that day was deemed to be equivocal and a contraction stress test was ordered. An oxytocin infusion was begun at a rate of 0.5 mU/min and gradually increased. Contractions began at a rate of 2.0 mU/min and were associated with persistent late decelerations from the start (Fig. 1). The oxytocin infusion was stopped and an ultrasonographic examination was performed. Fetal measurements were consistent with the menstrual gestational age of 35 weeks. Amniotic fluid volume was within acceptable limits. Of particular note was a large region of abnormal echogenicity involving the posterior fossa (cerebellum) and thalamus (Fig. 2).

Cesarean section was performed with the patient under epidural anesthesia. The amniotic fluid was clear

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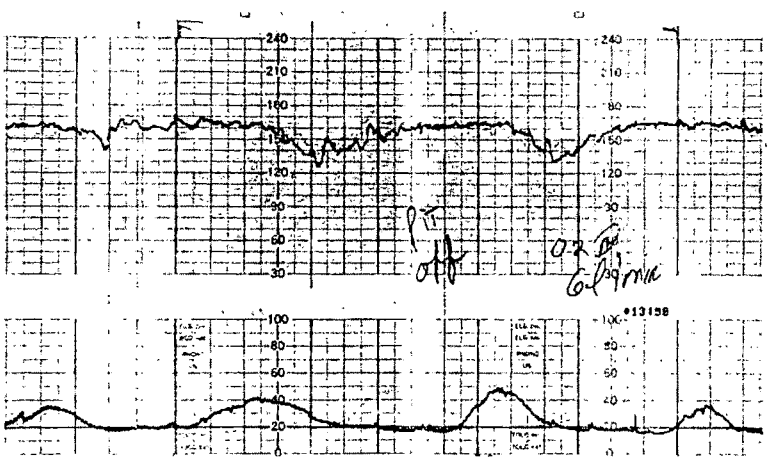


Fig. 1. Decelerations associated with oxytocin-induced contractions.

and there was no evidence of cord entanglement. The male infant who weighed 2693 gm and had a head circumference of 34.8 cm was described as pink with cyanotic extremities. He was limp and without reflex irritability or respiratory effort. Heart rate was less than 100 beats/min, resulting in a 1-minute Apgar score of 2. Cord blood gases were reported as pH 7.33 and pH 7.37 for arterial and venous blood, respectively. He was immediately intubated and given supported ventilation. His condition at 5 minutes was unchanged, resulting in an Apgar score of 2. Gasping respirations began at 65 minutes of age. Neither reflex nor spontaneous activity was present until 75 minutes of age when gradual spasmodic movements of the right arm and leg began, progressing rapidly to tonic-clonic seizure activity.

Cranial ultrasonographic scan showed massive hydrocephalus and a large echogenic structure in the right temporal lobe and atrium, spreading medially into the vicinity of the upper brain stem. Xenon-enhanced computed tomography showed evidence of hemorrhage in the left cerebellar hemisphere and thalamus. There was also hemorrhage in both ventricles.

A pulsed lumbar cysternostomy and right frontal external ventricular drain placement were done during the first day of life. Despite supportive treatment, the infant alternated between episodes of ventricular tachycardia and profound bradycardia. He had progressive acidosis, hyperchloremia and anuria, and died at age 46 hours. Pertinent autopsy findings were paraventricular leukomalacia with intraventricular, intracerebellar, and subarachnoid hemorrhage. No arteriovenous malformation was noted.



Fig. 2. Antenatal ultrasonographic scan of fetal head shows large thalamic and posterior fossa echogenic mass.

Comment

Although the cause of the massive cerebellar hemorrhage must remain speculative, certain observations are pertinent. Hemorrhage occurred in a fetus with adequate placental support as evidenced by a birth weight that was concordant with his gestational age and cord blood gases within a normal range. The latter observation is also supported by his pink color at birth, which is inconsistent with hypoxia just before the birth. This underscores the ambiguities of the Apgar score, which is comprised of diverse elements. A low Apgar score is widely considered synonymous with perinatal asphyxia, a concept that is formalized by the ICD-9 coding scheme.[1]

"Fetal distress" is a term with equally universal usage and similarly arbitrary definition. Certainly a fetus who has had a massive cerebellar hemorrhage is in "distress" in the most meaningful sense of the term. However, to rigidly equate fetal heart decelerations that occur in conjunction with contractions with placental insufficiency and fetal hypoxia is questionable because it ignores the possibility that an intracranial pathologic condition may result in increased sensitivity to repeated head compression manifested by similar decelerations. The value of obtaining cord blood gas determinations in such instances is suggested, as well as the use of cranial ultrasonographic scan or other imaging techniques in selected cases.

Finally, given the tremendous medicolegal problems arising from antenatal and perinatal brain damage, consideration should be given to the continued reporting of cases in which such damage is diagnosed prenatally. This is particularly the case for lesions commonly interpreted as occurring during birth and being traumatic in origin, as is cerebellar hemorrhage.[2]

We recognize our deceased colleague, Charles M. Hohler, MD, who performed the prenatal examinations.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. JULIAN T. PARER, San Francisco, California. The authors have presented a well-documented case of fetal intracranial hemorrhage that occurred at about 35 weeks' gestation, before the onset of labor, in an infant born subsequently by cesarean section.

I would like to discuss this article from two points of view: first, the individual case, and second, the broader implications, such as incidence.

The cause of this intracerebellar hemorrhage is not clearly evident. Possibilities include trauma, asphyxia, infection, and congenital defects, such as vascular anomaly or blood dyscrasia.

There is not evidence for trauma but this may not rule it out. An intriguing report from New Zealand has suggested that trauma may not have to be particularly severe because there is a substantial increase in intracranial hemorrhages in Pacific Islanders among whom abdominal massage late in pregnancy is an established custom.[1]

The site of the lesion does not support asphyxia as a cause. Conversely, there is evidence from the mother's assessment of decreased fetal movement for several days before intervention. This could conceivably have indicated an episode of severe asphyxia, which resulted in the hemorrhage, and then resolved sufficiently to result in normal umbilical cord pH at birth. The role of the late decelerations is puzzling. Although the presence of late decelerations at the time of a contraction stress test does not preclude the subsequent birth of an infant with normal blood gas levels, it does suggest that resting uterine blood flow (without uterine contractions) is just adequate to ensure fetal oxygenation.

We are not given information regarding the ruling out of infection in this case, but perhaps Dr. Jennett can tell us if such data are available. The exact role of infection in such intracranial bleeding as presented here is not well established. However, in a series of 25 autopsy reports from near term stillbirths, all with intracranial hemorrhage or gliosis, Sims et al.[2] found evidence of infection in 36% of cases.

Congenital conditions explaining this case are lacking. A tantalizing aspect of the patient's family history is in her father's and sibling's early death and morbidity, respectively, in their 30s of cardiovascular causes. Another aspect of the case is the role of cigarette smoking.

In summary, the cause of the intracerebellar hemorrhage in this case is unexplained.

Some of the broader implications of this case have been outlined. The incidence of this condition can be approximated from the series reported by Sims et al.[2] They found prelabor intracranial hemorrhage and gliosis in about 6% of stillbirths. Stillbirth occurs in less than 1% of pregnancies, thus such a condition may occur in approximately 5 per 10,000 pregnancies. In contrast to this, legal suit is filed in such cases in close to 100% of cases, so it is critical that such cases be appropriately diagnosed, as was done in this case with fetal ultrasonography, to ensure than the health care providers are not inappropriately blamed for misdiagnosing intrapartum fetal asphyxia.

We do not always have the luxury of such data, but we do have the possibility of ruling out intrapartum asphyxia in almost all cases. Intrapartum asphyxia can be ruled out if (1) the umbilical arterial acid-base state and blood gases are normal, (2) the Apgar score is normal (above 7 at 5 minutes), (3) there is normal fetal heart rate variability within several minutes of delivery, and (4) seizures do not occur in the first day or two of life.

The authors ruled out intrapartum asphyxia with cord blood acid-base state studies.

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DR. PETER WATSON, Portland, Oregon. I concur with Dr. Parer's remarks about the importance of obtaining cord blood gas levels whenever there is an abnormal fetal heart rate tracing and the possibility of an abnormal outcome. Obtaining cord blood gas levels helps much more than it hinders us in those medicolegal circumstances when it is very difficult to determine cause and effect.

I would like to suggest maternal cocaine abuse as a possible cause for the neonatal outcome in this case. The incidence of maternal cocaine abuse is rising and its association with intracerebral bleeding is well documented.[1] I wonder if a drug screen was obtained in this case. A drug screen is obtained in our institution in the event of any unexplained fetal or neonatal bleeding. A maternal urine sample positive for cocaine in this particular situation would not only explain the circumstances but would also do much to avoid litigation.

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DR. RUSSELL LAROS, San Francisco, California. Along the same line, Dr. Jennett, I assume laboratory studies were done on the infant to study the whole variety of coagulation abnormalities that could explain the bleeding. You did not mention platelet count, congenital hypofibrinogenemia, or congenital hypoprothrombinemia. Were all clotting factors evaluated and

was the mother questioned about the use of antiplatelet agents, such as aspirin or diuretics?

Dr. Jennett (Closing). We have agonized over this case and greatly appreciate the suggestions that have been made concerning possible causes. Dr. Parer, I can measure the interval with a calipers and say that there is no question that these are late decelerations. They do not fit any other category. There was not a great length of time between discontinuation of oxytocin, reduction of contractions, and the cesarean section. I keep trying to think of an imaginative explanation that would prove the experts wrong and demonstrate late decelerations caused by head compression. This woman smoked heavily and her cigarette smoking was a source of a great deal of concern to us. Unfortunately, I cannot quote statistics on the incidence of intracerebellar hemorrhage.

Dr. Watson asked about blood gas levels. I suppose with our worry and consternation, the blood gas laboratory ran only the cord pHs. However, the umbilical cord was immediately catheterized and the blood samples obtained showed no deviation from accepted levels of carbon dioxide and oxygen. The infant was definitely not metabolically acidotic. Your question of maternal drug use, especially of cocaine, is certainly an intriguing and pertinent one. In this case, no drug screen was obtained. Our hospital has wrestled with the question of performing drug screenings without permission and it has unfortunately decided that such screenings will not be allowed. We have good reason to believe that in our affluent area, cocaine usage is greater than in many areas, such as Los Angeles, that get a "bad press."

Dr. Laros, no history of the use of antiplatelet medications was sought and no coagulation studies were done.

Myomectomy as a reproductive procedure

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This series of 64 myomectomies describes the indications, technique, and efficacy of the procedure; the majority of operations were performed on large multinodular uteri. Indications included enlarging pelvic mass, menorrhagia, anemia, and pregnancy wastage in women who wished to preserve reproductive capability. Although infertility was not the primary indication in any case, 32 patients were nulligravid. Only 10 patients were parous and 14 had a history of spontaneous abortion or pregnancy wastage. The average age of the patients was 35.8 years (range, 27 to 47 years). There were no major complications and no patients received blood transfusions. Follow-up revealed three patients with recurrent tumors necessitating repeat procedures. Successful pregnancies have occurred in 40% of those attempting pregnancy. It is concluded that successful myomectomy can be performed in most patients regardless of uterine size, thereby preserving reproductive potential. (Am J Obstet Gynecol 1990;162:1476-82.)

Key words: Myomectomy, fertility, fibroids

Although myomectomy was introduced to gynecologic surgery nearly 150 years ago, it has been during recent years that it has become an increasingly important procedure performed with greater frequency. This increased use of myomectomy rather than hysterectomy results from the desire and necessity of patients to retain or improve reproductive potential. There are several reasons for this, the most important of which follow. Today there are generally fewer adoptive infants available to the infertile couple or patient after hysterectomy than in the past. Delaying attempts at pregnancy until a later maternal age has exposed many women to the increased prevalence of uterine myomas before conception. Finally, there is no current medical treatment to accomplish the permanent removal or resolution of uterine leiomyomas. In addition to these reasons, many women (whether they plan to attempt pregnancy or not), for various psychologic, emotional, or cultural reasons, are reluctant to proceed with hysterectomy and wish to preserve the uterus.

Despite the reason, and limiting discussion primarily to the groups wishing to attempt subsequent pregnancy, the role of myomectomy as a reproductive-enhancing or -preserving procedure is clearly established.

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Material and techniques

This article reports the experience of 64 myomectomies performed in 63 patients by the authors between Jan. 1, 1981, and Nov. 30, 1988 (Table I). The age range for the group was between 27 and 47 years, (average age, 35.8 years). Table II shows the number of procedures performed in 5-year age groupings.

Indications for myomectomy are shown in Table III. All patients were first seen with a pelvic mass, and the size of the uterus or a recent enlargement was the primary indication for surgery in 58 cases (uterine size, 12 weeks' gestational size or larger). In 37 patients, uterine size or recent continued growth was the only indication. These were instances in which the uterine size was usually significantly larger than 12 weeks' gestational size, and delay of myomectomy would result in a more difficult procedure, or in which the clinical setting suggested that subsequent attempts at achieving a successful pregnancy outcome would be jeopardized (e.g., cavity distortion, advanced maternal age, rapid growth of myomas). Ten patients had experienced 14 spontaneous abortions but only in four patients were the fibroid tumors thought to be directly related to the early pregnancy loss.

Infertility was not the primary indication in any patient, although 35 patients were nulligravid. The remaining 28 patients had been pregnant a total of 46 times, and 11 patients had been delivered 15 infants. There was a total of 15 spontaneous abortions; 11 occurred in 10 nulliparous women.

Table IV shows the comparative previous reproductive histories between those patients who attempted pregnancy after operation and those who did not. The

Table I. Myomectomies performed by year

Year	*No. performed*
1981	1
1982	5
1983	5
1984	8
1985	9
1986	16
1987	9
1988	11

Table II. Myomectomy ($N = 64$)

Patient age (yr)	*No.*
25-29	4
30-34	21
35-39	26
40-44	12
≥45	1

Age range 27-47 years; average 35.8 years.

Table III. Indications for surgery myomectomy

	No.
Pelvic mass	64 (58*)
Menorrhagia	4
Anemia	8
Pregnancy wastage	4
Spontaneous abortion	10
Pelvic inflammatory disease	9
Endometriosis	3
Previous sterilization	1
Septate uterus	1

*Primary indication.

Table IV. Premyomectomy reproductive performance

	No.
Patients attempting pregnancy ($n = 32$)	
Nulligravid	16
Gravid	16
Parous	4
Spontaneous abortion	7
Pelvic inflammatory disease or endometriosis	11
Patients not attempting pregnancy ($n = 27$)	
Nulligravid	18
Gravid	9
Parous	5
Sontaneous abortion	4
Pelvic inflammatory disease or endometriosis	1

only significant difference was that there were more patients with accompanying pelvic inflammatory disease or endometriosis in the group attempting pregnancy.

Operative techniques

Although myomectomy is a procedure that has been performed by gynecologic surgeons for many years, a few comments on preoperative preparation and operative techniques are appropriate. Because most of the operations in this series were performed before gonadotropin-releasing hormone agonists were readily available to most clinicians, they were not used preoperatively in any case to induce shrinkage of tumors before operation as has been suggested.[1]

Preoperative hysterosalpingography is desirable in nearly all cases. This allows definition of cavitary involvement and identification of interstitial obstruction of the fallopian tubes or associated distal tubal disease if it is present. If intracavitary fibroid tumors are present, or if it is likely that the uterine cavity will be entered, a dark solution of indigo carmine or methylene blue should be instilled into the uterine cavity before incision. This is most easily accomplished by a transcervical cannula or catheter. This greatly aids in determining when the cavity has been entered and assists in avoiding undue damage to the endometrial surfaces.

It has been our belief that vigorous attention must be paid to hemostasis to allow the surgeon to carefully and accurately remove all tumors, reconstruct the myometrial defects, and obtain meticulous closure of the uterine incisions. Therefore whenever possible we place a circumferential lower uterine segment tourniquet consisting of a size 12-Fr red rubber catheter cinched tight with hemostats. This is not released until the uterine incisions are being closed or are closed. There have been no cases of postoperative shock as a result of accumulation of a histamine-like substance as suggested by Rubin[2] and Ranney and Frederick,[3] and we do not think that it is a potential cause of ischemic damage, as mentioned by Buttram and Reiter.[4] We also employ the liberal use of a vasoconstrictive agent (vasopressin, 20 units in 200 ml of sterile saline solution), injected into the myometrium surrounding the fibroid tumors. Use of thes ancillary procedures allows the surgeon to work in a nearly bloodless field.

Careful thoughts should be given to the placement of the uterine incisions. Midline uterine incisions are generally less vascular, but incision placement should be made so that as many tumors as possible can be removed through a single incision while avoiding the uterotubal junction. The greater concern of posterior uterine incisions, which may cause complicating adhesions more frequently, is not as important with the ac-

Table V. Number and weight of fibroids removed

	No. of fibroids	*Weight of fibroids (gm)*
Total series (n = 64)	1-29 (Average 5.0)	100-765 (Average 284)
Patients wtih uterine size as only indication (n = 37)	1-10 (Average 4.1)	110-765 (Average 345.5)

Table VI. Postmyomectomy reproductive performance: pregnancies per age group

Patient's age (yr)	*No. of pregnancies*
25-29	0
30-34	8 (E, E, Ab)
35-39	3
40-44	5 (G, G, Ab)
≥45	0

E, Ectopic; *Ab*, spontaneous abortion; *G*, gamete intrafallopian transfer pregnancy.

complishment of meticulous closure of the serosal incision.

Our choice of suture material for the myometrial reconstruction is 2-0 or 4-0 Vicryl (Ethicon, Inc., Somerville, N.J.) for the deeper layers and 4-0 or occasional 6-0 Vicryl for the uterine serosa. In general, as small a suture as possible is used, but the suture should be large enough to avoid breaking or cutting through the tissue if placed under significant tension.

Procedures for actual removal of the myomas use familiar techniques of blunt and sharp dissection with conventional instruments. We use loupe lens magnification in many instances, because it emphasizes careful dissection. Vigorous traction on the tumors should be avoided, particularly when they are located close to the endometrial cavity or interstitial tube.

During the course of the procedure the pelvis is irrigated with Ringer's lactated heparin solution, and before closure of the peritoneum, 100 ml of dextran 70 (Hyskon, Pharmacia Laboratories, Piscataway, N.J.) is instilled in the cul-de-sac. Routine antibiotics or corticosteroids or other agents to prevent adhesions were not used.

Results

During the interval of the study, myomectomy was successfully performed in all patients for whom it was scheduled. Hysterectomy, hypogastric artery ligation, or other procedures to control bleeding was not necessary in any case. The average length of hospital stay was 4 days (range, 2 to 7 days); this is consistent with most laparotomies. There were no major complications, such as pelvic abscesses or bowel obstructions, that necessitated additional lengths of stay. Only three of the 64 procedures necessitated a hospital stay of over 5 days. The range of operating time of 55 minutes to 3 hours 50 minutes (average, 2 hours) generally correlated with the number of tumors removed or with ancillary procedures performed.

Because of strict attention to hemostasis, no patient required blood transfusion. Estimated blood loss ranged between 200 and 400 ml, and the average drop in hematocrit 24-hours after operation was six points.

There was a wide range in the total number and total weight of myomas removed (Table V). Larger tumors were removed from the group of patients in whom uterine size was the sole preoperative indication.

Thirty-two of the patients have attempted to become pregnant after operation. For a variety of reasons, 27 of the women have elected not to attempt pregnancy at this time; the most common reason is that they were unmarried. Two patients have had subsequent hysterectomies, and current information is not available for two patients.

Of the 32 patients who attempted pregnancy, sixteen have achieved a single pregnancy. Twelve of these have resulted in term viable infants (40%). There have been two ectopic pregnancies (both in patients with associated pelvic inflammatory disease), and two pregnancies that ended in spontaneous abortions. The sixteen pregnancies that occurred are shown related to maternal age at time of delivery in Table VI. Half the patients who were delivered were age 35 years of age or older and five were age 40 or older. Two patients became pregnant by gamete intrafallopian transfer.

There was no correlation between the total weight of fibroid tumors removed and the likelihood of becoming pregnant. The average fibroid tumor weight of those who subsequently conceived was 224 gm, and in those who did not conceive average tumor weight was 190 gm.

Of the 62 patients for whom follow-up data are available, recurrent myomas have been detected in four (6.4%). The reappearance of tumors occurred after 5 years in three patients and after 4 years in one patient. These have resulted in hysterectomies in two cases and repeat myomectomy in one patient. The remaining case is currently being followed up.

Comment

This series of myomectomies was collected and presented to illustrate several points. Sixty-one of the 63 patients in the study were either attempting pregnancy or wished to preserve childbearing potential for the future. Within this group, we estimate that 20% to 25% of the cases were either referred or sought second opinions because other physicians recommended hysterectomy as a first choice or told them that there was no alternative. To the contrary, if subsequent pregnancy

is even a consideration, hysterectomy is not an alternative. Even with the advanced degree of sophistication of assisted reproductive technologies allowing pregnancies to occur without fallopian tubes or even ovaries, a successful pregnancy is not possible without a uterus.

In view of this, myomectomy must be offered to this large segment of patients, and should be performed with the same principles of atraumatic technique used in other fertility operations. This implies careful hemostasis, accurate closure and reapproximation of uterine incisions, and magnification when necessary to avoid damage to delicate uterotubal structures and to minimize postoperative adhesion formation. This point cannot be overemphasized; Berkely et al.[5] concluded that myomectomy itself may decrease fertility, probably as a result of adhesion formation.

The question of whether fibroid tumors cause infertility was not addressed directly in this series, although subsequent reproductive function is of primary interest. After operation 50% of the patients who attempted pregnancy have succeeded (16 of 32). This figure may be somewhat decreased by the fact that six of the 16 patients who did not become pregnant in this group had either chronic pelvic inflammatory disease or endometriosis in addition to leiomyomas.

Infertility alone was not the primary indication for operation in any case, but it is likely that some of the patients were indeed infertile. Although disagreement exists regarding the extent of the relationship between fibroid tumors and infertility, several recent studies[5-8] have reported on myomectomy as treatment for infertility, with pregnancy rates ranging between 50% and 65.2%, similar to those reported here.

Berkely et al.[5] reported only seven of 21 patients over the age of 30 who achieved pregnancy after myomectomy, whereas 18 of 29 patients under age 30 conceived; Babaknia et al.[6] reported that they had no pregnancy successes in women over the age of 35. However, in our half of the patients who became pregnant were 35 years of age or older, and 32% (5 of 16) were 40 years of age or older. These findings are similar to those of Rosenfeld[8] who reported that five of eight patients over age 35 and two of four patients over age 40 became pregnant. We found no significant difference in the total weight of fibroid tumors removed and achievement in pregnancy, which differs from the findings of Berkely et al.,[5] who found average total weight of fibroid tumors in those who ultimately conceived to be 194 gm compared with 384 gm in those who did not.

The possibility of recurrence of leiomyomas is a clinical consideration, especially when myomectomies are performed in younger women. In an extensive review by Buttram and Reiter,[4] 493 (15%) of 2554 patients had recurrent myomas, with 330 (10%) requiring subsequent treatment. In 62 patients for whom we have accurate follow-up data, four patients (6.4%) have had recurrent tumors and operation was required in three (4.8%). A rather short length of follow-up may account for these lower rates, but we attempt to remove all tumors encountered regardless of size.

In summary, the importance of the role of myomectomy in preserving reproductive capacity is emphasized. This implies that the procedure be available to every patient desiring it, and that it be performed in a manner that minimizes postoperative complications that could decrease desired results. Sixteen of 32 patients who attempted pregnancy succeeded, and half were aged 35 or older. The total weight of tumors removed did not correlate with pregnancy success. It is our conclusion that virtually any patient in the reproductive age range, regardless of uterine size, is an appropriate candidate for consideration for myomectomy.

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Editors' note: This manuscript was revised after the discussions were presented.

Discussion

Dr. Howard A. Blanchette, Berkeley, California. Drs. Smith and Uhlir addressed a clinical problem that we as gynecologists confront daily in our practices. The challenge to preserve reproductive potential of women in the childbearing age group who are afflicted with leiomyomas necessitates myomectomy in any woman desirous of retaining her childbearing potential, or wishing to preserve her uterus for personal or cultural reasons.

The authors have emphasized the necessity to use the principles of infertility microsurgery in performance of myomectomy. They include preoperative evaluation with a hysterosalpingogram to allow definition of cavitary involvement and identification of interstitial obstruction of the fallopian tubves, or associ-

ated distal tubal disease. They also recommend instillation of indigo carmine or methylene blue into the uterine cavity before incision, to help in determining when the cavity has been entered. Intraoperatively a tourniquet is used circumferentially around the lower uterine segment and vasopressin, 20 units in 200 ml of sterile saline solution, is used liberally. Loupe lens magnification is also used. Fine suture material, ranging from 2-0 to 6-0 Vicryl, and meticulous attention to hemostasis is emphasized. Incisions are made in such a manner as to remove as many tumors as possible through a single incision, and serosal incisions are neatly closed. Intraoperatively the pelvis is irrigated with Ringer's lactated heparin solution; 100 ml of Hyskon is instilled in the cul-de-sac before closure of the peritoneum. Drs. Smith and Uhlir do not use routine antibiotics, corticosteroids, or other agents to prevent adhesions, nor do they use gonadotropin-releasing hormone agonist preoperatively to decrease vascularity and size of the uterus.

The results are impressive: 64 myomectomies over a time span of 7 years with no major complications, no blood transfusions, no intraoperative hysterectomies, average length of hospitalization of 4 days, 6.4% incidence of recurrent tumors, and, in those patients who attempt pregnancy, a 50% pregnancy rate with a 40% live-birth rate. Half of the pregnancies were in women over the age of 35.

Comparative results from my three-person private practice in obstetrics and gynecology in Berkeley substantiate these findings. Sixty-nine myomectomies were performed in a 10-year period from 1979 through 1989. There was little difference between the authors' patients and our patients with regard to previous reproductive performance, average age, indications for surgery, length of hospitalization, preoperative and postoperative hematocrit levels, numbers of tumors removed, and the weight of tumors removed.

However, differences were evident between the two groups in the use of hemostatic adjuncts. The authors routinely used a tourniquet and vasopressin, whereas in my group over a third did not have any hemostatic adjunct. This may have explained why three of our patients required intraoperative transfusion. Fourteen of our patients, contrasted with three of the authors' patients, had a length of stay greater than 5 days. The authors had no major complications, and we had two. One patient had postoperative endometritis that necessitated use of parenteral antibiotics, and another patient required intraoperative hysterectomy, not because of bleeding, but because the myomatous process was so extensive that meticulous excision would not preserve her childbearing potential. Four of our patients had excision of tumors that weighed more than 765 gm, which was the authors' upper limit; of interest is the one patient who had a 30-week size uterus, nine fibroids, with accumulative weight of 2640 gm. Sixteen percent of our patients had recurrent tumors, contrasted with 6.4% of the authors' cases.

The postmyomectomy reproductive performance in those patients who attempted pregnancy was similar in both groups; their group achieved a 50% pregnancy rate, and a 40% live birth rate, and our group achieved a 52% pregnancy rate with the same live birth rate. Half of their patients and one third of our patients who achieved pregnancy were over the age of 35.

The authors have stated emphatically that if a subsequent pregnancy is even a consideration in any woman with uterine leiomyomas, hysterectomy is not an alternative. They concluded that virtually any patient in the reproductive age range, regardless of uterine size, is an appropriate candidate for consideration for myomectomy. Recent studies in the literature addressing the enhancement of preoperative assessment and intraoperative management to improve the reproductive outcome of myomectomy include: (1) the preoperative use of magnetic resonance imaging to assess size and location of the fibroids, (2) the use of a gonadotropin-releasing hormone agonist preoperatively to reduce vascularity and size of the leiomyomas, (3) the use of the laser intraoperatively to improve hemostasis, reduce postoperative adhesion formation, remove myomas from previously inaccessible areas, and effect direct vaporization of smaller myomas, and (4) the judicious use of prophylactic antibiotics in instances when it is anticipated that the uterine cavity may be entered during the performance of myomectomy.

Controversy does abound in the literature regarding leiomyomas, infertility, and the role of myomectomy. I will outline the controversy by asking Dr. Smith the three following questions. (1) Should myomectomy precede attempts at conception if a documented submucous fibroid tumor is present? (2) At what uterine size should myomectomy precede attempts at conception? (3) In instances when a leiomyoma is the only finding in a couple's infertility evaluation, should myomectomy be performed?

Dr. Robert Israel, Los Angeles, California. In May 1935, Victor Bonney, consulting gynecologic and obstetric surgeon to the Middlesex Hospital, London, England, was the invited guest at the American Gynecological Society's annual meeting in Hot Springs, Virginia. In 1946 he thanked the fellows of that Society by dedicating to them his new book, *The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy.*[1] On the basis of his experience with over 800 myomectomies, the focus of the book is directed toward the various operative approaches that can be used depending on the location and size of the myomas encountered. If Victor Bonney were alive today, he would be delighted with this paper that not only espouses myomectomy, but clearly demonstrates that this operation can be performed with precision and attention to detail that will yield very low complication and recurrence rates.

Recent years have seen a great improvement but radical operations on the womb are still being carried out where conservatism would be equally feasible and safe; the surgeons who perform them being either timid of new ways or too confirmed

in the old, to change. I have no message for the suture-bound, nor for those whose capacity is already stretched to its utmost, but to those others I would say that surgery thus shorn of what should be its chief adornment, mercy, is a mean goal to aim at.[1]

Having praised the authors' study for its vision and excellent results, I would like to raise some questions and review some concepts that, hopefully, will make this an even stronger paper. As noted by the authors, all 64 patients who had myomectomies presented with a pelvic mass, and in 58 uterine size or a recent enlargement were the primary indications for operation. How many of the 58 cases were in each of these categories? Additionally, when does size become an indication? Although the authors discuss tumor weight, they did not mention what is clinically important preoperatively: uterine size. What was the breakdown of these cases by uterine size and how was "recent enlargement" evaluated? This information would seem to be relevant since none of the patients apparently presented with clinically important pain, pressure symptoms, or excessive bleeding.

Because combined surgical procedures often yield poorer results, one wonders whether the patient who underwent myomectomy with reversal of tubal sterilization maintained tubal patency and conceived? In the patient who underwent transabdominal myomectomy and metroplasty, where was the myoma(s) located, and, if it did not involve the uterine cavity, was consideration given to a hysteroscopic metroplasty to prevent the future need for cesarean section?

With no major complications, no blood transfusions, and the normal postoperative length of stay, it is obvious that we cannot quarrel with the authors' meticulously thorough operative technique. Bonney would be proud.

I have often thought how wonderfully perfect the surgery of the abdominal cavity would become, if we could send a team of trained Lilliputians down a ladder through the abdominal wound with instructions to get on with the job. What gentleness! What absolute hemostasis! What meticulous neatness of adjustment and suture! How little after-pain; not worse than a mild toothache. What safety! Gentleness is of great importance in myomectomy, for the hurried wrenching out of deeply-imbedded tumours shocks the patient and mauls the tissues.[1]

Drs. Smith and Uhlir for Lilliputians-of-the-Year!

The average drop in the postoperative hematocrit was 6 points. With the hemodilution usually observed after operation when 100 ml of dextran 70 are left in the pelvis, this hematocrit fall is not unusual. When was the postoperative hematocrit sample drawn?

Were the 12 infants who were born after myomectomy delivered vaginally or by cesarean section? If there were any cesarean sections, were they performed because the uterine cavity had been entered, or a significant portion of the myometrium violated, at the time of myomectomy? All the myomectomies were performed between 1981 and 1988. With the low rate of myoma recurrence, how many patients were followed up for how long (i.e., how many have been followed up 8 years, how many 7 years, etc?).

Although all of the authors' cases involved uterine myomata, they were fortunate that on occasion they did not encounter an enlarged adenomyomatous uterus rather than an enlarged myomatous uterus. If the planned operation is a hysterectomy, differentiating between the two is unimportant. However, if the planned operation is a myomectomy, finding adenomyosis when the uterine wall is incised leaves only one conservative alternative: Back out, closing the abdominal incision as you go. Fortunately, today we have magnetic resonance imaging that can differentiate between adenomyosis and myomas *before* operation. With use of a high index of suspicion, especially with a globularly enlarged uterus, preoperative magnetic resonance imaging, with even just a few sagittal views, will prevent you from starting a "myomectomy" on an adenomyomatous uterus. Could the authors explain their non–magnetic resonance imaging "skills" and could they also give their opinion on magnetic resonance imaging use?

Given the lack of any significant cases of menorrhagia, one wonders whether the Seattle weather does not permit the development of submucous myomas or, in actuality, there were no submucous lesions? The difficult myoma cases involve a combination of submucous myoma(s), menorrhagia, and anemia. With the clinical availability of at least one gonadotropin-releasing hormone agonist, the bleeding can be stopped, thus allowing the anemia to be corrected with iron therapy, and the myoma(s) can be reduced to a size that can be handled hysteroscopically or through a Pfannenstiel skin incision, in contrast to the authors' midline vertical approach. Although no blood transfusions were necessary in this study, they are potentially necessary in all myomectomies. Autologous blood use is the preferred method of intraoperative and postoperative blood replacement. Even in the patient with menorrhagia, the use of a gonadotropin-releasing hormone agonist can create an amenorrheic state and allow restoration of a normal hemoglobin level and the ability to self-donate blood.

In 1946, Victor Bonney[1] wrote: "Very few cases of fibroids are now beyond the technical range of myomectomy. There is a pleasure, a pride, and a satisfaction in these conservative operations which cannot be appreciated save by those who have performed them, and I want to see them in the repertory of every surgeon called upon to operate on the womb."[1]

Forty-three years later, Bonney would revel in Smith and Uhlir's last sentence: "It is our conclusion that virtually any patient in the reproductive age range, regardless of uterine size, is an appropriate candidate for consideration for myomectomy."

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Dr. Smith (Closing). All questions posed by Drs. Israel and Blanchette are important and appropriate; however, time constraints preclude addressing most of them. I will comment briefly on a few of their questions.

To clarify Dr. Israel's comments, we do not use vertical abdominal incisions. The incisions I alluded to are vertical uterine incisions. In regard to the use of magnetic resonance imaging for the definition of myoma as opposed to adenomyosis, I believe that use of ultrasonography and pelvic examination, together with presenting complaints, is sufficient to differentiate between the two disease entities and is more economical. In our series we have encountered adenofibromas but no frank cases of adenomyosis.

With regard to Dr. Blanchette's three questions, I have no definite answers to these clinical dilemmas. In a patient with a submucous myoma, unless it marked distorts the cavity, an attempt at pregnancy is probably justified before myomectomy. Although the age of the patient, size of the fibroid tumor, and the total clinical setting must be considered, I have seen patients with prominent lower-segment fibroids carry pregnancies to term.

At what uterine size do we choose to intervene? There is no definite answer. I believe that uterine sizes larger than 12 to 14 weeks' gestational size begin to be more technically difficult, and allowing the uterus to grow beyond this point may produce a more difficult procedure. I would perform a myomectomy at that time, even if the patient was going to defer pregnancy attempts to some later date.

The last question regards the infertile patient and fibroid tumors. If you think your evaluation is complete, no other cause has been uncovered, and more conservative therapeutic approaches have been unsuccessful, then, and only then, should myomectomy be considered.

Pregnancy rates with fresh versus computer-controlled cryopreserved semen for artificial insemination by donor in a private practice setting

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From late 1970 through December 1987, 580 women began 733 treatment programs (a total of 3405 insemination cycles) with fresh semen for artificial insemination by donor. The unadjusted pregnancy rate was 48.5% and the cumulative pregnancy rate after seven cycles by life-table analysis was 59.6% with a monthly fecundability of 11.9%. From 1988 to the present, 113 women have begun 115 treatment programs (a total of 371 insemination cycles) with cryopreserved semen for artificial insemination by donor. The unadjusted pregnancy rate to date is 18.3% and the cumulative pregnancy rate after seven cycles by life-table analysis is 48.6% with a monthly fecundability of 5.9%. This report shows that using cryopreserved semen for artificial insemination by donor will take somewhat longer to produce a pregnancy but the ultimate pregnancy rate will be similar to that with fresh semen for artificial insemination by donor. (AM J OBSTET GYNECOL 1990;162:1483-90.)

Key words: Artificial insemination by donor, fresh artificial insemination by donor, cryopreserved artificial insemination by donor, pregnancy rates

Artificial insemination by donor (AID) has been practiced at The Fertility Institute since late 1970. During most of this time fresh semen was used. This required the careful timing of donor and patient appointments, made weekend inseminations impractical, and often led to disappointment in patients when donors were unavailable for subsequent pregnancy attempts. In 1987 we began the use of a computerized staged-freezing technique for the purpose of semen cryopreservation. Our initial intention was to use cryopreserved semen as a "backup" to make AID more readily available and convenient for our patients and to provide an opportunity for a controlled comparison of the efficacy of fresh versus frozen semen. However, the American Fertility Society published recommendations in February of 1988 advising against the use of fresh semen for artificial insemination because of the increased risk of sexually transmitted diseases (particularly acquired immunodeficiency syndrome).[1] As of that date *only* cryopreserved, 6-month quarantined specimens have been used for AID in our program.

The resulting abrupt switch from using fresh semen to using cryopreserved semen did not allow us the opportunity to do a study controlling all variables and using the patient as her own control with alternating cycles of fresh or cryopreserved semen for insemination with the purpose of comparing the pregnancy rates achieved. Because of this, many factors do vary between the two populations studied. For example, when AID was begun in our practice in 1970, basal body temperature measurement was the standard means of ovulation detection with two inseminations per cycle recommended to cover the time of ovulation. As technology improved, luteinizing hormone measuring became more readily available to pinpoint ovulation more accurately and inseminations were often decreased to once per cycle. Consequently many AID cycles with fresh specimens had two inseminations to adjust for a less accurate predictor of ovulation time while cycles with cryopreserved specimens usually had one very carefully timed insemination. Although these methodologic changes over the years result in groups that are not strictly comparable, we felt that it was nevertheless useful to make retrospective comparisons between the pregnancy rate with fresh semen (inseminations done between 1970 and 1988) and that using cryopreserved semen (1988 to the present). This article makes that comparison and discusses possible reasons for the differences that exist.

Material and methods

A treatment program is defined as a series of one or more essentially sequential monthly cycles of insemi-

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Table I. Age distribution, gravidity, and parity of patients undergoing AID with either fresh or cryopreserved semen

	Fresh semen (%)	*Cryopreserved semen (%)*
Age distribution (yr)		
≤24	7.1	2.6
25-34	70.6	51.3
≥35	22.3	46.1
Gravidity and parity		
G0	46.4	43.5
G ≥ 1, P0	26.9	26.1
G ≥ 1, P ≥ 1	26.7	30.4

nation in one patient for the purpose of achieving a pregnancy. From late 1970 through December 1987, 580 women began 733 treatment programs of artificial insemination with fresh donor semen (consisting of from one to more than 20 cycles) at The Fertility Institute (Infertility, Gynecology and Obstetrics Medical Group of San Diego) for the purpose of achieving a pregnancy. From January 1988 to the present, 113 women have begun 115 treatment programs of artificial insemination with cryopreserved semen (consisting of from one to ten cycles) for the purpose of achieving a pregnancy. The patients in both groups ranged in age from 20 to >40 years old. Some had never been pregnant while others had achieved previous pregnancies (Table I). The two groups of women were not different in terms of their reproductive history ($p > 0.20$ by χ^2 analysis), but the treatment group that received cryopreserved semen for AID was significantly older ($p < 0.001$ by χ^2 analysis) than the group that received fresh semen for insemination. Infertility workups were generally begun only after 6 months of failed AID but ovulation was always documented in insemination cycles. Some patients were in the midst of their treatment programs when the switch was made from fresh to cryopreserved semen. These patients were included in the fresh AID study group for all cycles in which fresh AID was done. They were not, however, included in the cryopreserved AID study group since they could not be regarded as new patients beginning a treatment program. There have been several pregnancies from cryopreserved AID in this group of patients who had previous cycles of fresh AID. These pregnancies are not included in any of the statistics in this report.

Donors were recruited from the local medical and graduate school programs, and these donors were required to meet all of the standards recommended by the American Fertility Society in the policy statement entitled Minimal Genetic Screen for Gamete Donors.[2] Donors were always initially and periodically tested for sexually transmitted diseases and, subsequent to the publication of the New Guidelines for the Use of Semen for Donor Insemination (American Fertility Society[3]), all testing recommended therein was performed. This included the quarantining of all frozen semen for 6 months, after which time the donor was retested for sexually transmitted diseases (especially human immunodeficiency virus) before the specimens were released for use.

Cryopreservation of semen was performed by adding to the liquified semen either 10% glycerol (Sigma Chemical Co., St. Louis) or an equal volume of Test-Yolk buffer solution (Irvine Scientific, Irvine, Calif.). Aliquots of the semen mixture were put into plastic Nunc vials and cryopreserved in a controlled temperature freezing chamber (model 1010 controller and model 990C freezing chamber; CryoMed, Mt. Clemens, Mich.). The temperature was lowered at 1° C/min to −4° C sample temperature (ramp 1), 25° C/min to −40° C chamber temperature, and then 15° C/min to −12° C chamber temperature (ramps 2 and 3, to allow for sample latent release of heat), 1° C/min to −40° C chamber temperature (ramp 4), and finally 10° C/min to −90° C (ramp 5). At the end of the freezing cycle the vials were plunged into liquid nitrogen where they remained until use.

Either one or two inseminations were performed in the periovulatory period as timed by basal body temperature measurements or luteinizing hormone testing. Inseminations with cryopreserved specimens were always timed by luteinizing hormone testing to define more precisely the time of ovulation since there is some concern that frozen-thawed sperm may have a shorter time of viability. Insemination occurred approximately 24 hours after the detection of a luteinizing hormone surge. Each intracervical insemination consisted of either an entire fresh specimen or a cryopreserved specimen containing a minimum number of motile sperm. Although each fresh specimen did not have a sperm count, specimens were periodically checked to ensure a sperm count of at least 30 million per milliliter with 50% motility. However, vagaries of fresh semen usage are such that it is unlikely that every specimen used for every patient met these criteria. Until February 1989 each cryopreserved specimen was required to have at least 12.5 million motile sperm after thawing. If a specimen did not meet this criterion, additional vials were thawed until the minimum was met. After February 1989 the minimum was increased to 20 million motile sperm after thawing. A few cycles consisted of intrauterine inseminations of washed sperm if indicated by the patient's diagnosis. With fresh semen the entire specimen was washed, while with cryopreserved semen the prewash motile sperm count was at least 20 million before February 1989 and 40 million after that date. This very small number of intrauterine insemination

Table II. Results of AID treatment programs by number of completed cycles

No. of cycles	*No. of treatment programs*	*No. lost to follow-up*	*No. of pregnancies*	*No. stopped AID*	*No. continuing AID*
Fresh semen					
1	180	39	107	33	1
2	121	24	72	18	7
3	81	14	35	28	4
4	81	24	32	21	4
5	62	13	34	14	1
6	49	15	18	14	2
7	30	7	12	9	2
8	15	3	5	6	1
9	23	5	8	8	2
10	16	4	9	3	0
>10	75	20	24	30	3
TOTAL	733	166	356	184	27
Frozen-thawed semen					
1	25	2	6	11	6
2	26	3	4	5	14
3	21	1	4	3	13
4	17	1	2	3	11
5	8	0	1	1	6
6	9	0	2	1	6
7	6	0	2	0	4
8	1	0	0	0	1
9	1	0	0	0	1
10	1	0	0	0	1
TOTAL	115	7	21	24	63

patients was not separable from the "plain" AID specimens in our data collection method and they have been included in the statistics for their respective groups (fresh versus frozen).

Comparisons of the pregnancy rates for inseminations with fresh versus frozen semen were made by the statistical methods described in detail by Cramer et al.[4] Life tables (limited to the first 10 insemination cycles since data for AID with cryopreserved semen are not yet available beyond that point) were constructed and monthly fecundabilities were determined. The Z test was used to compare the monthly fecundabilities and χ^2 analysis was used for other comparisons.

Results

Table II gives the results of the two treatment programs listed by the number of insemination cycles completed by each patient. For the patient population receiving fresh semen for insemination, there were 356 pregnancies among 733 treatment programs started for an unadjusted pregnancy rate of 48.5%. These 733 treatment programs included a total of 3405 insemination cycles for an average monthly fecundability of 10.5%. For the patient population receiving cryopreserved semen, there were 21 pregnancies among 115 treatment programs started, for an unadjusted pregnancy rate of 18.3%. These 115 treatment programs included a total of 371 insemination cycles, for an average monthly fecundability of 5.7%.

The life-table analyses for the cumulative probability of pregnancy from AID with either fresh or cryopreserved semen are shown in Tables III and IV. In Table III the cumulative probability of pregnancy from AID with fresh semen reaches 59.6% at seven cycles and 67.9% at 10 insemination cycles. This life-table analysis estimates the monthly fecundability as 11.9% with a 95% confidence interval of 10.6% to 13.1%. In Table IV the cumulative probability of pregnancy from AID with cryopreserved semen reaches 48.6% at seven insemination cycles, and the number of patients undergoing more than seven cycles is so small that interpretation beyond that point is not statistically valid. The life-table analysis estimates the monthly fecundability as 5.9% with a 95% confidence interval of 3.4% to 8.4%. The difference in fecundability between AID with fresh semen versus AID with cryopreserved semen is significant by the Z test ($p < 0.001$).

Fig. 1 depicts the cumulative probability of pregnancy after AID with either fresh or frozen semen. For the patient population receiving fresh semen the probability of pregnancy is 16.2% after one insemination cycle and rises slowly to 59.6% after seven cycles. The probability of pregnancy for those patients inseminated with cryopreserved semen, which also rises slowly but

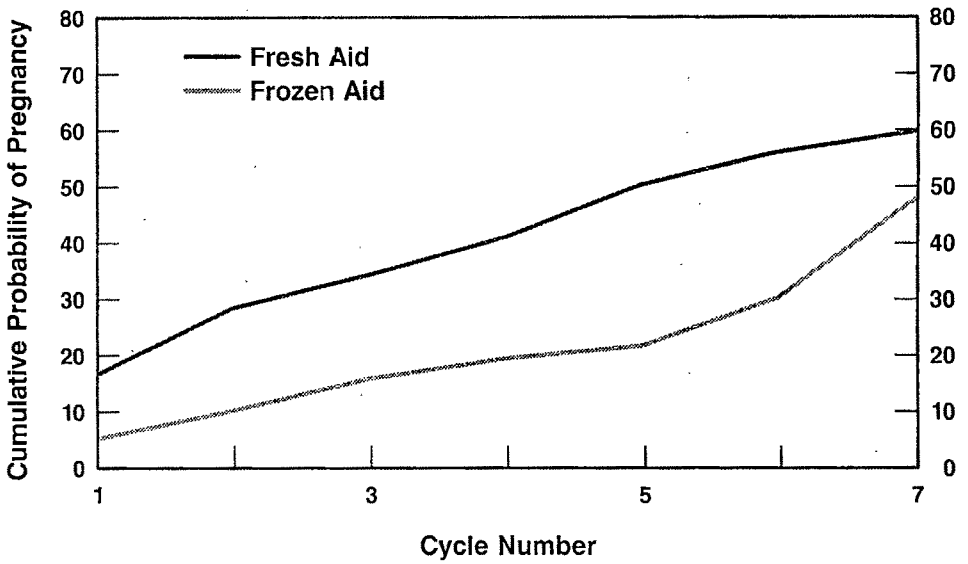


Fig. 1. Cumulative probability of pregnancy from AID with fresh or frozen semen: Life-table analysis.

is always less than that found after the same number of cycles using fresh semen, is 5.4% after one cycle and climbs to 48.6% after seven cycles. The difference between the cumulative probabilities of pregnancy with fresh or cryopreserved semen after seven insemination cycles (59.6% vs 48.6%) is of borderline significance ($0.02 < p < 0.05$ by χ^2 analysis).

Comment

When our program of semen cryopreservation began, we sought to optimize the cryopreservation techniques used. A computer-controlled staged freezing apparatus was used since it had been demonstrated that such a freezing protocol was superior to simple vapor freezing.[5] Glycerol was used as the cryoprotectant because of its demonstrated effectiveness, ease of availability, and small effect on the volume of the specimen.[5,6] After some experience with the 10% glycerol freezing protocol, we chose to switch to a commercially available cryoprotectant containing yolk buffer in the hope of improving the postthaw recovery of sperm motility.[7] Although this cryoprotectant does necessitate the 1:1 dilution of the semen specimen, we have found it to be superior to 10% glycerol since the recovery of motile sperm is greater. Initially we used a minimum acceptable number of motile sperm after thawing for an insemination of 12.5 million mainly because of the limited supply of quarantined specimens. As our inventory increased, this was raised to 20 million on the basis of indications that this might significantly increase the chances for achieving pregnancy.[8,9]

Monthly fecundability rates for inseminations with fresh semen reported in the literature range from slightly above 10% to >25% while the rates for inseminations with cryopreserved semen are somewhat lower, ranging from 5% to about 15%.[7,9,10-13] Our results are comparable to those in these reports.

In this study the overall unadjusted pregnancy rate for AID with cryopreserved semen is considerably lower than that for AID with fresh semen (18.3% vs 48.5%). This difference in the study is artificial and is explained by the fact that AID with cryopreserved semen is a fairly recently begun and ongoing study while the fresh AID study is complete. This is demonstrated by the fact that in the study of AID with cryopreserved semen 60% of the patient's treatment programs are still ongoing with fewer than six insemination cycles completed while at the termination of the study with fresh semen less than 5% of the treatment programs were still ongoing with fewer than six completed cycles. Thus 60% of the patients in the cryopreservation program have not yet had a "fair try" at AID and should therefore not be viewed as treatment failures. This information and that found from the life-table analyses lead us to believe that the overall pregnancy rates for AID with fresh versus cryopreserved semen will be comparable but that it will take more insemination cycles to achieve that overall pregnancy rate when cryopreserved semen is used. This conclusion is further supported by the fact that the treatment group that received cryopreserved semen is significantly older ($p > 0.001$) than the group that received fresh semen. Since the overall fertility rate decreases as a woman ages, it is likely that the difference in the cumulative pregnancy rates, independent of patient's age for fresh versus cryopreserved semen used for AID, is even smaller than our results suggest.

In the hope of further improving the pregnancy rate

Table III. Cumulative probability of pregnancy from AID with fresh semen: Life-table analysis

Cycle No. i	*Observed at start of cycle* Ni	*No. of pregnancies* Ci	*No. lost to follow-up* Li	*Person months of follow-up* Ti = Ni − (Ci + Li)/2	*Probability of pregnancy per cycle* f = Ci/Ti = Pi	*Probability of no pregnancy in cycle* 1-Pi	*Cumulative probability of pregnancy* Fi = 1 − m(1 − Pi)
1	733	107	39	660	0.162	0.838	0.162
2	553	72	24	505	0.143	0.857	0.282
3	432	35	14	408	0.086	0.914	0.344
4	351	32	24	323	0.099	0.901	0.409
5	270	34	13	247	0.138	0.82	0.515
6	208	18	15	192	0.094	0.906	0.561
7	159	12	7	150	0.08	0.92	0.596
8	129	5	3	125	0.04	0.96	0.612
9	114	8	5	108	0.074	0.926	0.641
10	91	9	4	85	0.107	0.893	0.679

Table IV. Cumulative probability of pregnancy from AID with frozen semen: Life-table analysis

Cycle no. i	*Observed at start of cycle* Ni	*No. of pregnancies* Ci	*No. lost to follow-up* Li	*Person months of follow-up* Ti = Ni − (Ci + Li)/2	*Probability of pregnancy per cycle* f = Ci/Ti = Pi	*Probability of no pregnancy in cycle* 1 - Pi	*Cumulative probability of pregnancy* Fi = 1 − m(1 − Pi)
1	115	6	2	111	0.054	0.946	0.054
2	90	4	3	87	0.046	0.954	0.098
3	64	4	1	62	0.065	0.935	0.156
4	43	2	1	42	0.048	0.952	0.197
5	26	1	0	26	0.039	0.961	0.228
6	18	2	0	17	0.112	0.888	0.314
7	9	2	0	8	0.25	0.75	0.486
8	3	0	0	3	0	1	0.486
9	2	0	0	2	0	1	0.486
10	1	0	0	1	0	1	0.486

per cycle when cryopreserved semen is used, we plan to further increase the number of motile sperm used per insemination since recent studies have shown increasing pregnancy rates as the motile sperm number is increased to ≥40 million.[7,9] It is important to realize that because of the increased specimen volume created by the cryoprotectant used for freezing and the resulting impracticality of performing an insemination with the entire number of sperm present in a single fresh ejaculate, by definition all frozen inseminations provide a lesser average number of motile sperm than do fresh specimens. It seems likely that the lower fecundability rate of frozen specimens per cycle is largely due to the fact that fewer total motile sperm are used per insemination rather than to any intrinsic deficiency introduced into the surviving sperm by the freezing process. This decreased total motile count per specimen is theoretically correctable by using only donors with unusually high initial counts and good thaw survival characteristics to increase the number of motile sperm per cryopreserved semen insemination. Unfortunately this approach is limited by the relative scarcity of such donors. Another possible approach, which has been used successfully elsewhere, would be to inseminate with a higher number of motile sperm and to concentrate the specimen by centrifugation before freezing if the volume is too great.[7] It must be kept in mind, however, that there is always a loss of sperm during a centrifugation step.

Because of the retrospective and purely clinical nature of this study, the population groups have not been controlled for variables such as patient age, potential causes of infertility, or gravidity and parity. Table I does examine the relative occurrence of some of these factors; however, as the patient group receiving cryopreserved semen completes the study, these variables will be examined in more detail.

In conclusion, artificial insemination with semen specimens cryopreserved with a computerized staged freezing technique, where the minimum postthaw total motile sperm count was 12.5 to 20 million, has been retrospectively compared to insemination with fresh semen specimens. The fecundicity rate per cycle is less for the frozen specimens (5.9% vs 11.9%, $p < 0.001$), but the difference in the cumulative probabilities of pregnancy after fresh or cryopreserved semen inseminations after seven cycles is of borderline significance (59.6% vs 48.6%, $0.02 < p < 0.05$). Since the group that received cryopreserved semen specimens is significantly older ($p < 0.001$), this difference is likely to be artifactual. Thus, with frozen specimens prepared in this manner, it will take somewhat longer to achieve a pregnancy but the ultimate pregnancy rate for the two populations should be the same. Careful preselection

of donors for semen cryopreservation to maximize the postthaw sperm counts so that the minimum number of motile sperm used per insemination will more closely approach the "normal" of fresh specimens may reduce or eliminate the apparent difference in the fecundicity rate per cycle between the two methods.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Kenneth A. Burry, Portland, Oregon. This paper by Dr. Young and his colleagues is timely and important to those of us who treat infertile couples. Artificial insemination by donor is a well-accepted procedure to overcome infertility because of a severe male factor. The risk of transmitting AIDS warrants strict guidelines for the selection of donors and the preparation and use of semen.

Cryopreservation of semen is successful, allowing storage of semen for an indefinite period. Most centers quarantine semen for 6 months and release it for use if the donor remains seronegative for HIV. It is assumed that 6 months is an adequate time to follow up the donors.

The risk of using frozen semen is the possibility of not achieving pregnancy. Richter et al.[1] report lower fecundity rates with frozen semen than with fresh semen. Dr. Young's paper also reports a monthly fecundability of frozen semen to be one half that of fresh semen, 5.9% compared with 11.9%. The cumulative pregnancy rates were different after seven insemination cycles; however, the authors downplay this difference because of the age differences between the two groups of patients. The cumulative probability of pregnancy reported in this paper is 0.486 at 10 months for frozen semen and 0.515 at 5 months for fresh semen. Therefore with more cycles of insemination the pregnancy rates are similar, but it takes twice as much time.

The number of total motile sperm used for insemination is a critical factor. In this article Dr. Young reports on the use of 12.5 to 20 million motile sperm. Nielsen et al.[2] define 20 million motile sperm as the minimum number. These authors had no pregnancies when <12 million motile sperm were used. Comparing fresh with frozen semen, Bordson et al.[3] found no decrease in fecundability when using a total of 40 million, grade 3, motile sperm. Hammond et al.[4] used 60 million motile sperm with similar results; however, the fecundity was low in both groups of patients. Brown et al.[5] demonstrated a significant increase in fecundability with >100 million motile sperm compared with <100 million motile sperm.

The site of insemination may be another critical factor in fecundability rates. Similar fecundability rates occur with eight times fewer sperm with an intrauterine site of insemination. With fresh semen, Patton et al.[6] report a fecundability of 0.185 with an intracervical site and 151.2 ± 20.6 million motile sperm. In comparison, the fecundability of an intrauterine insemination was 0.148 with 18.3 ± 2.9 million motile sperm. It is important to know the number of total motile sperm before insemination, especially if a sperm wash-rinse was done. Intrauterine insemination with a minimum of 24 million motile sperm resulted in a monthly conception rate of 0.24. The conception rate was not further increased by doubling the sperm number.[7] At the Oregon Health Sciences University, a prospective study comparing intracervical insemination, intrauterine insemination, and intratubal insemination is being done. The site of insemination and the critical number of sperm required to achieve pregnancy within the shortest time are the questions to be answered.

I would like to ask Dr. Young the following questions:

1. How many women were inseminated with 12.5 million motile sperm and how many were inseminated with 20 million motile sperm? Were there enough women in each group to compare fecundability rates?
2. Similarly, how many women were in each of the

two intrauterine insemination groups, 20 versus 40 million? Was there a difference between these groups?
3. How many women received intrauterine insemination versus intracervical insemination, and was there a difference?
4. How many inseminations were done per cycle?
5. What were the mean ages per group? It appears that the age difference between the groups is significant; however, there is a 10-year range between 25 and 34 years. More important, what were the ages of the women who conceived? Were pregnancy rates compared between age groups?
6. Was there a difference in ovulation problems requiring ovulation induction between the groups?
7. When do you evaluate tubal and peritoneal factors by hysterosalpingography and laparoscopy? In view of the longer time required to achieve a pregnancy with frozen semen, should the evaluation of these women be different than when fresh semen is used?
8. Finally, will you comment on the total number of motile sperm and possibly the site of placement of sperm as important factors in achieving pregnancy?

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DR. G. DAVID ADAMSON, Palo Alto, California. I have been performing donor insemination in my practice for 9 years. I used fresh sperm exclusively until February 1988 when the American Fertility Society revised its guidelines for donor insemination and recommended the use of frozen sperm. At that time, because of our concern over reduced fecundity with frozen sperm (to approximately 40% of that with fresh sperm in most studies in the literature), we decided to undertake a prospective randomized study comparing the pregnancy rates with fresh and frozen sperm. After approval by an investigational review board, we have conducted this study for the past year and a half. We screen donors for human immunodeficiency virus on a monthly basis with the polymerase chain reaction deoxyribonucleic acid gene amplification test, which costs about $200 per donor per month. We also screen for all sexually transmitted diseases every month. We feel that this provides a very safe situation for the patients. Data in the literature suggest the risk of human immunodeficiency virus infection is in the order of 1 in 500 million per insemination in this situation. So far our data show that fecundity is 19.6% per month with fresh sperm and 9.4% with frozen, a ratio of 48%.

The fecundity with frozen sperm being only half as high as that with fresh is a major issue. Most studies in the literature show that couples attempt donor insemination on average of only about four cycles. If you have to have eight cycles to get the same pregnancy rate with frozen sperm, many more couples will have discontinued treatment before being successful. The reduced fecundity also becomes an issue in patients who have reduced fecundity, for example, those with endometriosis, tubal disease, or older age. Dr. Young, have you any comments on the potential use of fresh sperm in these situations, especially in view of current diagnostic techniques for infectious diseases?

DR. FRED HANSON, Davis, California. Since 1974 we have had a large donor insemination program at the University of California, Davis. We also have had a fresh semen research protocol approved by our investigational review board, and our success rates are in line with those reported by Dr. Adamson.

Our group has been very concerned about differences in the span of time during which frozen and fresh sperm maintain the ability to fertilize an egg in vivo. This relates not only to the timing of insemination but also to the ability to withstand the laboratory preparation for intrauterine insemination. In our experience, some of our patients, who use the OvuQuick ovulation detection kit, already have ruptured follicles as determined by ultrasonography on the day of luteinizing hormone surge. When using frozen sperm, we are starting to switch to a policy of insemination both on the day of the color change and 24 hours later.

Dr. Young, I am concerned about the comparability of your two groups. Your change of freezing techniques makes the frozen sperm group actually two different groups. Did you do any intrauterine inseminations? It appears that some of your timing of insemination was by basal temperature graphs alone and some by luteinizing hormone surge. Moreover, you changed the minimum required number of sperm per specimen; and in some cases you did two inseminations rather than a single insemination per cycle. Each of these factors could have a profound impact on success rates.

DR. YOUNG (Closing). It is interesting that two centers have been able to obtain permission for studies involving fresh semen. I personally thought that the American Fertility Society acted precipitately in issuing the February 1988 statement saying that fresh semen

should not be used at all. The risk of transmitting acquired immunodeficiency syndrome is very small and can be very carefully controlled. For that matter, no one really knows if a 3- or 6-month quarantine guarantees a specimen free of the human immunodeficiency virus. A prospective randomized clinical trial with fresh and frozen specimens is thus very appropriate.

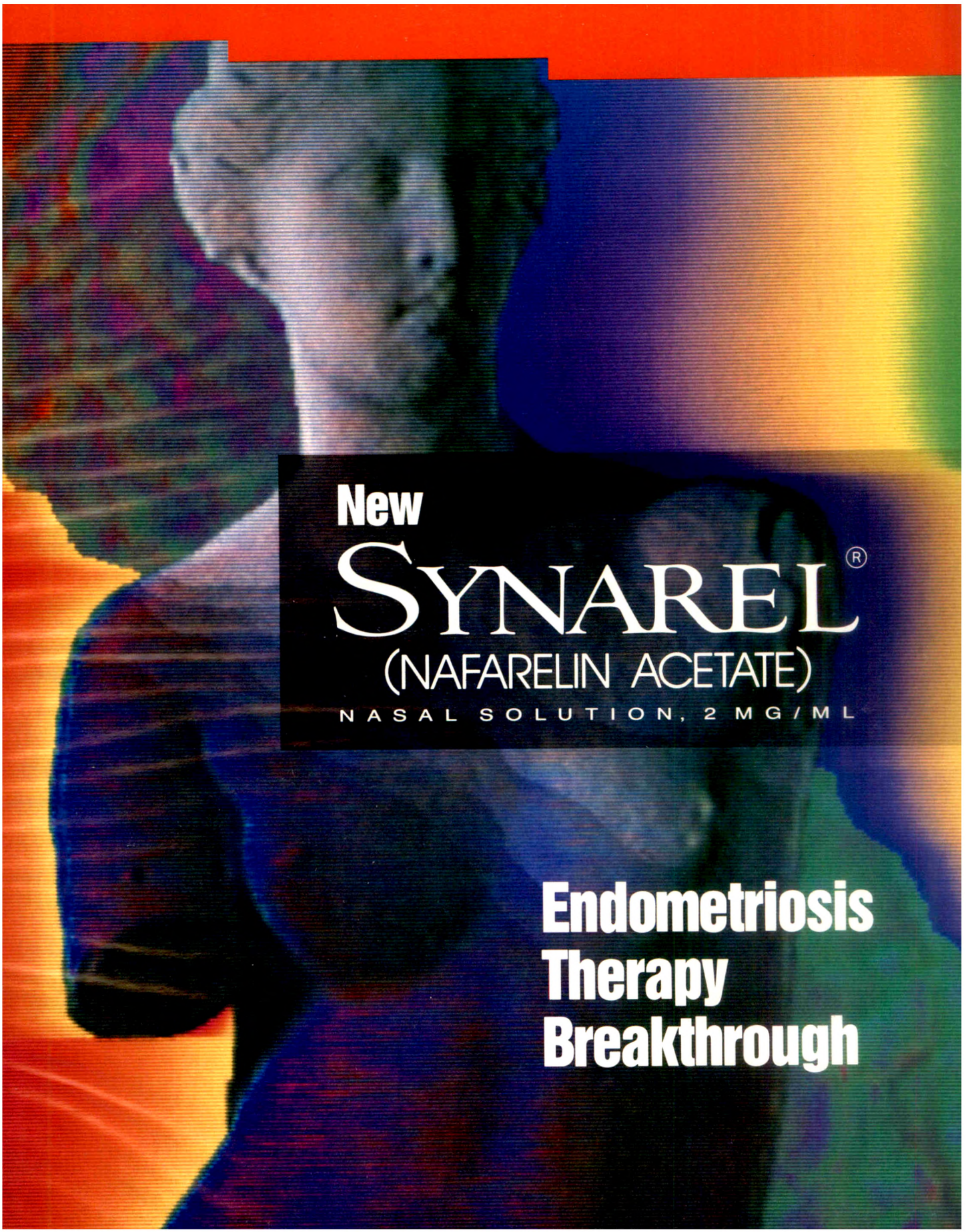
I believe that in two clinical situations the use of fresh semen is appropriate. (1) Couples who have arranged a woman surrogate for insemination have no wish to use frozen specimens and neither does the surrogate. (2) For the occasional couple who have personally arranged a known donor for one reason or another, I also use fresh semen. I regard these two situations as having the same risks as having intercourse with the semen donor. We have these people sign stacks of waivers and go ahead with fresh inseminations. We do test the donor but we do not require that his specimen be frozen.

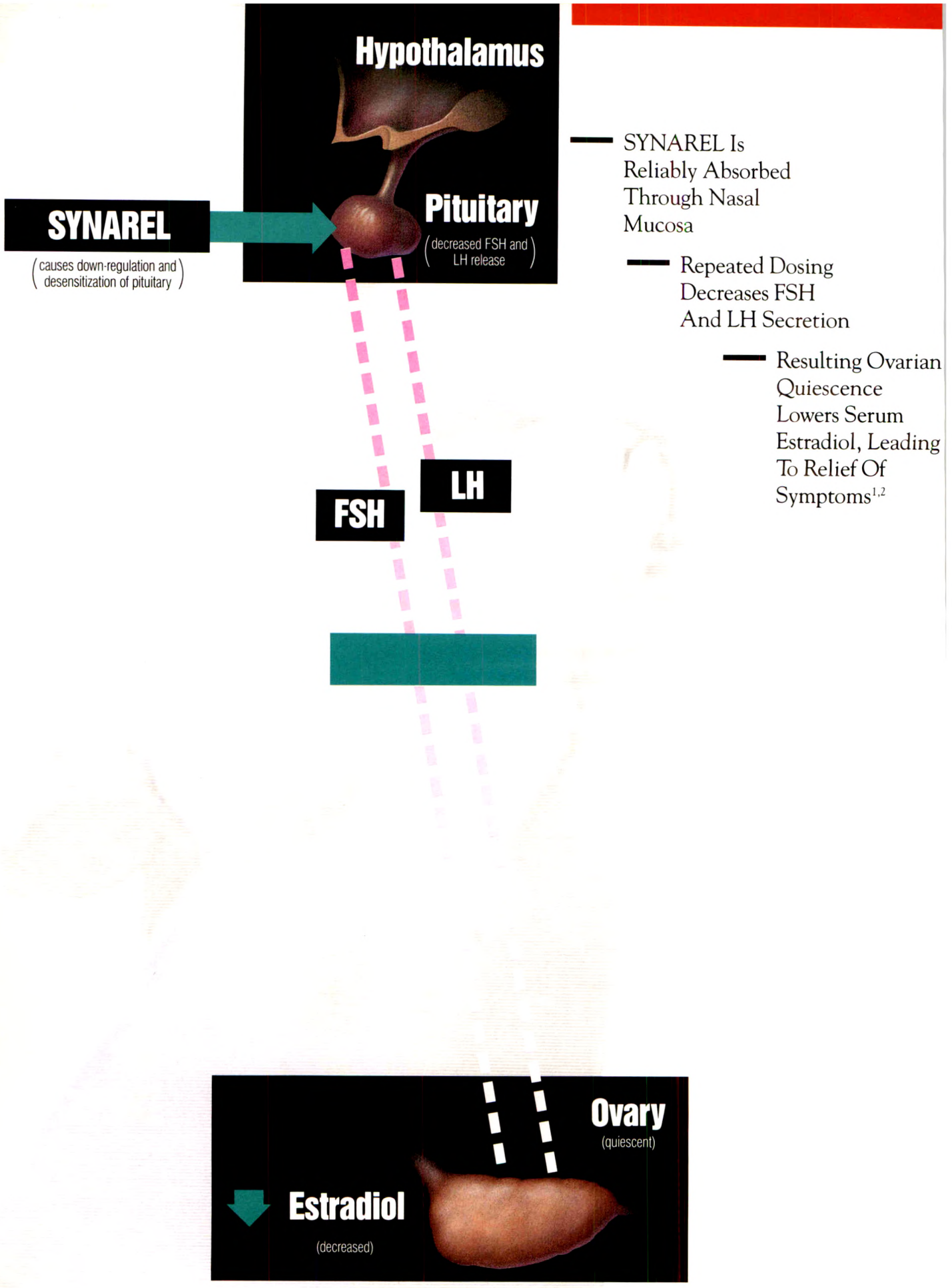
We changed our minimum total count for insemination from 12.5 to 20 million when it was technically possible to do so. I would guess that at least half the patients had >20 million per milliliter and the other half had between 12.5 and 20. I'm disappointed that the change from 12.5 to 20 hasn't resulted in a more impressive change in pregnancy rates. I hope that the change will be more dramatic when we can get to 40 or 50 million per milliliter. We did not analyze the effect of the woman's age.

In view of the longer time required to achieve a pregnancy with frozen semen, one may well ask if the evaluation of the woman should be changed. We had routinely done diagnostic studies of women who failed to conceive after 6 months of inseminations with fresh semen. We knew that 70% or so of those who are going to conceive will have done so within that time. When we use frozen sperm, I believe that we should wait until 9 or 12 months, depending on the age of the patient.

I'm not impressed that intrauterine insemination solves many problems. Of course, if you can take a normal specimen, wash it, and get 24 million motile sperm to put in the uterus, I have no doubt that you'll have a very good pregnancy rate. In the infertile couple with a male factor or when one is using frozen specimens, that can't be done. The critical thing for artificial insemination is to improve our technology to get the maximum number of motile sperm for delivery to the cervix. There is nothing mysterious about that. Freezing technologies will improve so that we can do it. We should be able to find the number of motile sperm needed to make the pregnancy rate equal to that with fresh sperm.

Dr. Hanson, we use intrauterine insemination as the next step when cervical insemination has been deemed to fail, that is, after 6, 12, or 18 months, depending on the individual case. We have done only a few cases of intrauterine insemination with frozen sperm and are not impressed. We tend to move on quickly to something else at that point.


New
SYNAREL®
(NAFARELIN ACETATE)
NASAL SOLUTION, 2 MG/ML
Endometriosis
Therapy
Breakthrough



— SYNAREL Is Reliably Absorbed Through Nasal Mucosa

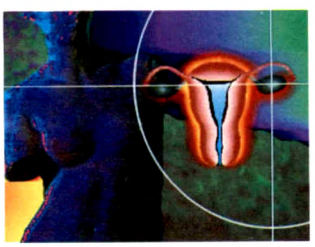
— Repeated Dosing Decreases FSH And LH Secretion

— Resulting Ovarian Quiescence Lowers Serum Estradiol, Leading To Relief Of Symptoms[1,2]

New SYNAREL® For Endometriosis
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The Only GnRH* Agonist Indicated For The Management Of Endometriosis

- **94% Of Synarel Patients Reported Improvement Of Symptoms**
- **86% Of Patients Showed Improvement Of Endometriotic Lesions**
- **Lowers Estrogen Without Adding Androgens**[1,2]
- **Significantly Fewer Masculinizing Side Effects Than Danazol** (The most frequent side effects are those associated with hypoestrogenism)
- **The Only GnRH Agonist Administered Intranasally**



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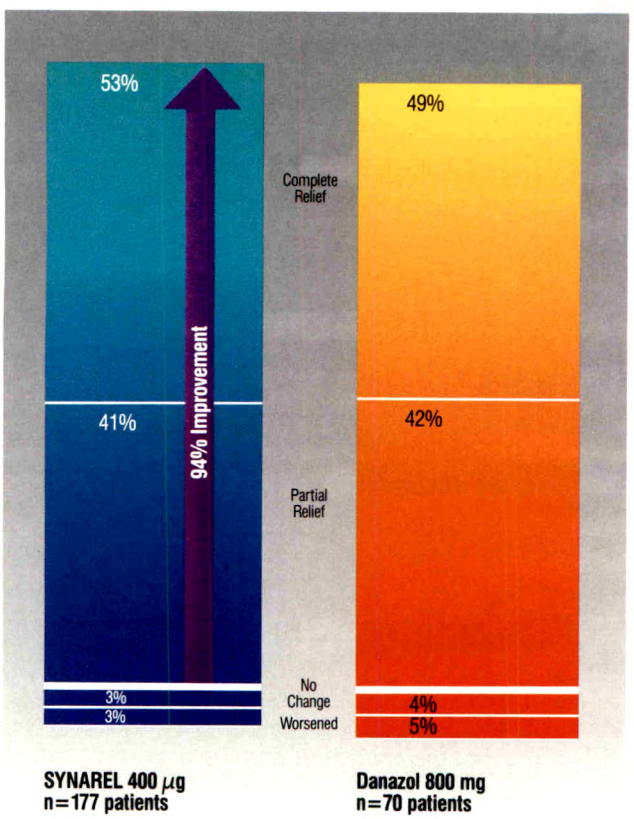
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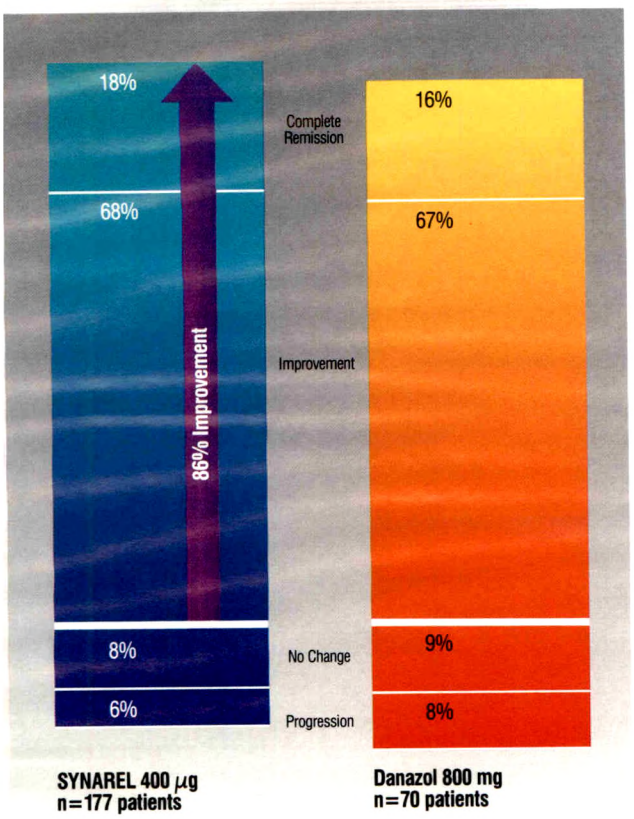
94% Of Synarel Patients Reported Improvement Of Symptoms



Changes in symptom severity scores from admission to end of study

- Relieves dysmenorrhea, dyspareunia and pelvic pain
- Sustained efficacy in 83% of patients 6 months post-treatment

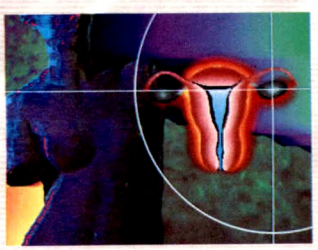
86% Of Patients Showed Improvement Of Endometriotic Lesions



Changes in laparoscopy scores from admission to end of therapy

- Post-therapy laparoscopy confirmed improvement in all stages† of endometriosis
- Number of patients in Stages III and IV decreased 42% and 57% respectively
- Retreatment cannot be recommended since safety data for retreatment are not available

†Based on American Fertility Society laparoscopy score stages: 0 (absent, score 0), I (minimal, 1–5), II (mild, 6–15), III (moderate, 16–40), IV (severe, >40).



New

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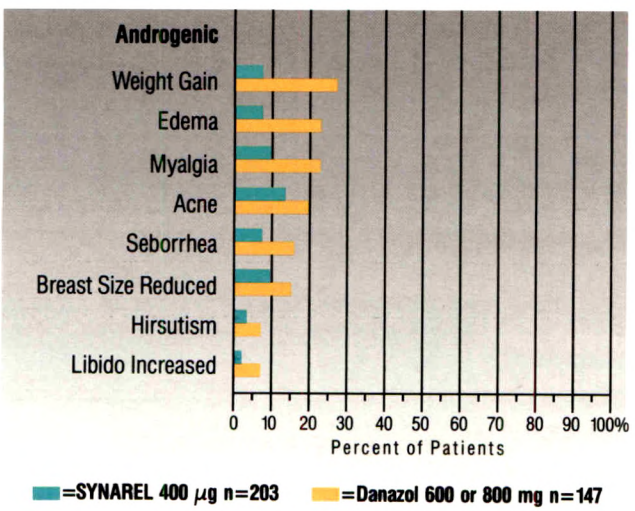
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New SYNAREL® For Endometriosis
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Lowers Estrogen Without Adding Androgens[1, 2]

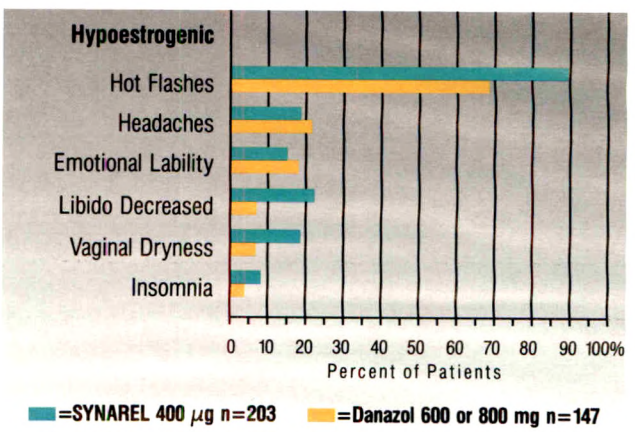
Synarel Exhibits Fewer Masculinizing Side Effects Than Danazol



Adverse events during 6 months treatment

- More frequent and/or severe with danazol:
  Weight gain
  Edema
  Acne
  Oily skin
  Hirsutism
- Some androgenic effects of danazol—such as voice deepening—may be irreversible[3]
- Patients should be advised to use non-hormonal methods of contraception when taking SYNAREL

Synarel Exhibits Predictable Hypoestrogenic Profile



Adverse events during 6 months treatment

- Estrogen levels return to normal after cessation of therapy
- Bone changes largely reversible 6 months post-treatment

Bone Density Changes During And After Treatment With SYNAREL (400 μg/day)

Site Method Units	Time of Study Baseline	End of Treatment	Post-treatment
Lumbar Vertebrae QCT,* Integral (g/vertebrae) n=21	13.4	12.8 −4.3%	13.1 −3.3%
Trabecular Bone of Vertebrae QCT* (mg/cc) n=23	161.3	147.6 −8.7%	152.0 −4.9%
Lumbar Vertebrae DPA† (g/cm^2) n=6	0.98	0.93 −5.9%	0.96 −1.4%
Distal Radius SPA** (Units) n=6	40.2	39.5 −1.6%	39.6 −0.8%

Percent changes from baseline

*Quantitative computed tomography
†Dual photon absorptiometry
**Single photon absorptiometry

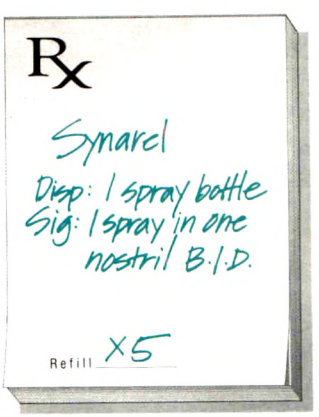
Intranasal Administration

Synarel Is The Only GnRH* Agonist Administered Intranasally

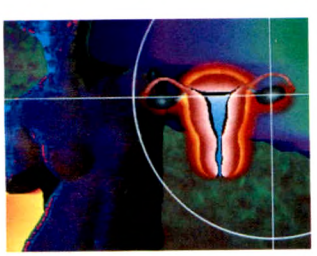


B.I.D. controlled-dose administration offers:

- Highly accurate metered-dose delivery—200 µg/spray
- Reliable absorption through nasal mucosa
- Patient convenience with low incidence of nasal irritation (10%)



For more information, please call
1-800-727-0400



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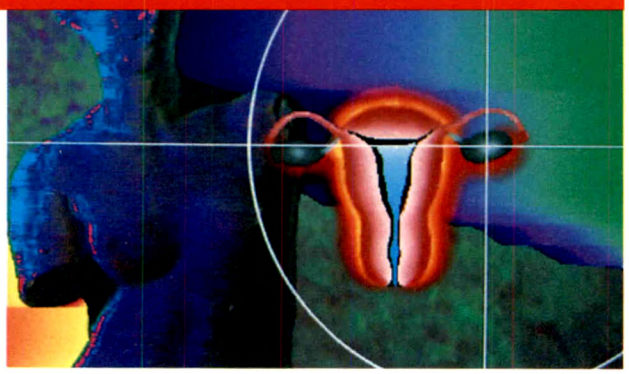
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NASAL SOLUTION, 2 MG/ML

*Gonadotropin-Releasing Hormone Analog

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New SYNAREL® For Endometriosis
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— The Only GnRH* Agonist Indicated For The Management Of Endometriosis

— Unsurpassed Resolution Of Pain And Endometriotic Lesions

— Fewer Masculinizing Side Effects Than Danazol (The most frequent side effects are those associated with hypoestrogenism)

— The Only GnRH Agonist Administered Intranasally

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*Gonadotropin-Releasing Hormone Analog

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829-G2-108-89

SYNTEX

SYNTEX LABORATORIES, INC
PALO ALTO, CA 94304

BRIEF SUMMARY

SYNAREL® Nasal Solution contains nafarelin acetate (2 mg/mL, expressed as nafarelin base), benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid, sorbitol, and purified water.

INDICATIONS AND USAGE: For management of endometriosis. Experience is limited to women 18 years and older treated for 6 months.

CONTRAINDICATIONS: Hypersensitivity to GnRH, GnRH agonist analogs or any excipients in SYNAREL; undiagnosed abnormal vaginal bleeding; pregnancy or possibility of pregnancy while taking the drug because SYNAREL may cause fetal harm when administered to a pregnant woman. If SYNAREL is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus; use in women who are breast feeding.

WARNINGS: Safe use in pregnancy has not been established clinically. Before starting treatment pregnancy must be excluded.

When used regularly at the recommended dose, SYNAREL usually inhibits ovulation and stops menstruation. Contraception is not insured, particularly if patients miss successive doses. Therefore, patients should use nonhormonal contraception. Advise patients to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, discontinue the drug; apprise patient of the potential risk to the fetus.

PRECAUTIONS Information for Patients: 1. Since menstruation should stop with SYNAREL, the patient should notify her physician if regular menstruation persists. Patients missing successive doses may experience breakthrough bleeding.

2. Patients should not use SYNAREL if pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of its ingredients.

3. Safe use in pregnancy has not been established. Therefore, a nonhormonal method of contraception should be used during treatment. If a patient becomes pregnant during treatment, she should discontinue the drug and consult her physician.

4. Adverse events occurring most frequently in clinical studies are associated with hypoestrogenism. Nasal irritation occurred in about 10% of patients.

5. Induced hypoestrogenic state results in a small loss in bone density over a 6-month treatment course. Some of this loss may not be reversible. During one six-month treatment period, this should not be important. In patients with major risk factors for decreased bone mineral content, i.e., chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, SYNAREL may pose additional risk. In these patients risks and benefits must be weighed carefully. Repeated courses of treatment with GnRH analogs are not advisable in patients with major risk factors for loss of bone mineral content.

6. Patients with intercurrent rhinitis should consult their physician for use of a topical nasal decongestant. If a topical nasal decongestant is required during treatment, it must be used at least 30 minutes after SYNAREL dosing to decrease the possibility of reducing drug absorption.

7. Retreatment cannot be recommended since safety data beyond 6 months are not available.

Drug Interactions: No pharmacokinetic-based drug-drug interaction studies have been conducted. Nafarelin acetate is a peptide primarily degraded by peptidase and not by cytochrome P-450 enzymes, and is only about 80% bound to plasma proteins at 4°C; therefore drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions: SYNAREL in therapeutic doses suppresses the pituitary-gonadal system. Normal function is usually restored 4–8 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions during treatment and up to 4–8 weeks after discontinuation of SYNAREL may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in rats and mice at intramuscular doses up to 110 times and 560 times the maximum recommended human intranasal dose, respectively. These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced hyperplasia and/or neoplasia of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies using bacterial, yeast, and mammalian systems provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when treatment was discontinued after continuous administration for up to 6 months.

Pregnancy, Teratogenic Effects: *Pregnancy Category X.* Intramuscular SYNAREL was administered to rats throughout gestation at about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration. An increase in major fetal abnormalities was seen in 4/80 fetuses at the highest dose. A similar study at the same doses in rats and studies in mice and rabbits at doses up to 600 μg/kg/day and 0.18 μg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration throughout gestation. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers: It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most frequently reported adverse reactions were those related to hypoestrogenism. In controlled studies comparing SYNAREL (400 μg/day) and danazol (600 or 800 mg/day), the following adverse reactions were most frequently reported and thought to be drug-related.

Hypoestrogenic: hot flashes (SYNAREL 90%, danazol 69%), decreased libido (22%, 7%), vaginal dryness (19%, 7%), headaches (19%, 21%), emotional lability (15%, 18%), insomnia (8%, 4%); **Androgenic:** acne (13%, 20%), myalgia (10%, 23%), reduced breast size (10%, 16%), edema (8%, 23%), seborrhea (8%, 17%), weight gain (8%, 28%), hirsutism (2%, 6%), increased libido (1%, 6%); **Local:** nasal irritation (10%, 3%); **Miscellaneous:** depression (2%, 5%), weight loss (1%, 3%).

Less than 1% of patients experienced paresthesia, palpitations, chloasma, maculopapular rash, eye pain, urticaria, asthenia, lactation, breast engorgement, and arthralgia. In clinical trials, immediate hypersensitivity thought to be possibly or probably related to nafarelin occurred in 3 (0.2%) of 1509 healthy subjects or patients.

Changes in Bone Density: After 6 months' treatment vertebral trabecular bone density and total vertebral bone mass, measured by quantitative computed tomography (QCT), decreased by an average of 8.7% and 4.3%, respectively, compared to pretreatment levels. There was partial recovery of bone density post-treatment; the average trabecular bone density and total bone mass were 4.9% and 3.3% less than pretreatment levels, respectively. Total vertebral bone mass, measured by dual photon absorptiometry (DPA), decreased by a mean of 5.9% at end of treatment. Mean total vertebral mass, re-examined by DPA 6 months post-treatment, was 1.4% below pretreatment levels. There was little, if any, decrease in the mineral content in compact bone of the distal radius and second metacarpal. Use for longer than the recommended 6 months or in presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Changes in Laboratory Values: *Plasma enzymes.* During clinical trials SGOT and SGPT levels were more than twice the upper limit of normal in only one patient each. There was no other evidence of abnormal liver function and levels returned to normal after treatment was stopped.

Lipids. At enrollment and at end of treatment, 9% of patients on SYNAREL 400 μg/day and 2% on danazol had total cholesterol values above 250 mg/dL.

Of those with pretreatment cholesterol values below 250 mg/dL, 6% on SYNAREL and 18% on danazol had post-treatment values above 250 mg/dL.

Mean (±SEM) pretreatment values for total cholesterol from all patients were 191.8 (4.3) mg/dL in the SYNAREL group and 193.1 (4.6) mg/dL in the danazol group. At the end of treatment, mean values from all patients were 204.5 (4.8) mg/dL in the SYNAREL group and 207.7 (5.1) mg/dL in the danazol group. These increases from pretreatment values were significant ($p < 0.05$) in both groups.

Triglycerides were increased above the upper limit of 150 mg/dL in 12% of the patients on SYNAREL and in 7% of the patients on danazol.

At the end of treatment, no patients on SYNAREL had abnormally low HDL cholesterol fractions (< 30 mg/dL) compared with 4.3% of patients on danazol. No patients on SYNAREL had abnormally high LDL cholesterol fractions (> 190 mg/dL) compared with 15% of those on danazol. There was no increase in the LDL/HDL ratio in patients on SYNAREL, but approximately a 2-fold increase in the LDL/HDL ratio in patients on danazol.

Other changes. In comparative studies, the following changes were seen in approximately 10% to 15% of patients. SYNAREL was associated with elevations of plasma phosphorous and eosinophil counts, and decreases in serum calcium and WBC counts. Danazol therapy was associated with an increase of hematocrit and WBC.

OVERDOSAGE: At present there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

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The computerized digital imaging colposcope: Future directions

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A computer-aided colposcope has been developed for enhancement and analysis of colposcopic images. There are numerous possible applications of this system, including image archiving, image enhancement and processing, and quantitative measurements of various features in the images. In addition, a wide range of digital filters can be applied to the system that may be used to detail different aspects of the image. The method for a new mode of applying digital and optical filters to the colposcope is discussed and future directions for the system are suggested. (AM J OBSTET GYNECOL 1990;162:1491-8.)

Key words: Colposcopy, computer imaging, image processing

Although the colposcopic evaluation of the female lower genital tract has been well established, the basic optical system of the colposcope has not changed since it was introduced by Hinselmann in 1925.[1] A brief historic outline of major developments related to colposcopy is shown in Table I. The static state of the present colposcope has limited its use to primary diagnosis of the abnormal Papanicolaou smear as a single event.

The potential scope of the "abnormal Papanicolaou smear" problem is enormous. Ten percent of sexually active Americans, approximately four million people, harbor the human papilloma virus (HPV). There are more than one million new cases of genital warts each year. There are now 57 varieties of HPV; most types are relatively harmless, but types 16 and 18 are carcinogenic.[2, 3]

The HPV problem necessitated that a new clinical approach was mandatory if the pathogenesis of these lesions was to be studied further. A system for computerized, enhanced image analysis, viewed and measured through a range of light sources, offers the possibility of a technique to improve our understanding of the cervical HPV lesion. This type of system was developed by Craine et al.[4]; similar techniques have since been used by other groups.[5]

In this article we discuss some of the basics of the system, indicate the nature of some of the experiments we are doing, and discuss some possible advantages that may emerge from use of the digital imaging techniques.

Table I. Milestones in the development of colposcopic diagnosis and treatment of cervical intraepithelial neoplasia

Year	*Development*
1924	Hinselman fixed a light source to a dissecting microscope (×3.5 magnification)
1925	Hinselman built the first colposcope, described surface carcinoma (cervical intraepithelial neoplasia)
1930	Introduction of the colpomicroscope
1940	Papanicolaou smear, thought to be competitive with the colposcope
1960	Cryosurgery introduced
1980	Laser surgery introduced
1988	Introduction of the first computer-aided colposcope

Material and methods

The digital imaging colposcope that we use is the DENCOL 2100, a prototype of which was described by Craine et al.[4] This system consists of a stock Zeiss photocolposcope (Carl Zeiss Inc., Thornwood, N.Y.) to which is attached an optical interface and a video format, solid state, two-dimensional charge-coupled device imager. The incoming image is transferred to the charge-coupled device by means of an optical beam-splitter in the colposcope and, with proper adjustment of the transfer optics, the scene viewed through the binocular eyepiece is identically transferred to the charge-coupled device. The chargecoupled device is a silicone-based device that offers a broad range of spectral response from the ultraviolet cutoff to the optical infrared.

An RS-170 format video signal is carried through a

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5 to 7 meter long coaxial cable to a digitizing board set residing in a host 80286 architecture microcomputer. The board set is a dual-frame buffer design that allows two digital images to be instantly available at all times for processing. The incoming video images are digitized at a spatial resolution of 512 × 480 px and a contrast resolution of 7 or 8 bits, depending on whether a graphics overlay plane is activated.

The host microcomputer supports a computer monitor (through a Hercules graphics card or its equivalent) and a video monitor; it is interfaced by a keyboard and a mouse. A 20 Mb hard disk provides nonarchival storage and a high-density (1.2 Mb) diskette drive is used for moving images to archival locations.

In addition to a variety of digital filters, discussed briefly below, it is thought that some advantage may be derived from use of multispectral optical filters in the system. We have initiated some preliminary experiments to address this issue and will discuss some aspects of those experiments in this article.

The system is completed by an application specific software package (COLPO) in a menu-driven format. This package allows a range of file manipulation functions, and some modest image processing and analysis functions. Experiments are underway to determine the most satisfactory form factors for the system and to explore a variety of image processing algorithms that might be most useful for clinical colposcopy applications.

The COLPO main menu currently consists of five basic menus: File, Acquire, View, Enhance, and Analyze.

The *File* menu enables the user to load, save, copy, rename, or delete images. In addition the user may elect this option to display an image directory or to quit the program.

The *Acquire* menu is selected if the user wants to digitize a live input image into either of the two onboard memory locations, or pages.

The *View* menu allows the user to display the current live image, or either of the two digitized images currently in the dual-frame buffers. An additional useful feature is that any set of images (live or digital) may be sequentially displayed on the video monitor at a user-selected frequency. The result is a video "blink comparator" system that rapidly and dramatically displays differences between similar, but perhaps subtly different, images (such as a series of images obtained in the course of monitoring a patient over a period of time). The *View* menu also allows the user to display or hide the graphics overlay plane.

The *Enhance* menu offers contrast enhancement control over the displayed image (either real-time live examination images or stored digital images), as well as a selection of 3 × 3 digital filters that can enhance contrast gradients or feature edges (such as boundaries to areas of dysplasia) or high-frequency features (such as blood vessels or punctation).

The *Analyze* menu allows use of a graphics overlay plane to calibrate and measure distances, perimeters, and areas of features of interest in the image. The user may also use this menu to annotate the image with text or symbols.

Our experimental software system has incorporated capabilities to add, subtract, and divide the digital images as well as apply additional digital filters to the colposcope images. These functions allow the user to extract subtle features of interest by reducing noise in the images, or by removing an unwanted background that may be cluttered or otherwise confusing in interpretation of the image. These functions may be particularly useful in combination with various digital and optical filters.

The conventional method for digital image capture with this system is as follows. The desired magnification for viewing is selected at the colposcope and a glass optical filter, if needed, is inserted in the outgoing light path (i.e., in the fiber optic illumination system). The scene of interest is selected either by visual observation through the colposcope or by monitoring the video display. At this point the user may elect to turn on the contrast enhancement and probe the dynamic range of the current live image. In any event, when a satisfactory image is displayed it may be digitized in a fraction of a second by a keystroke.

The digital image is then displayed and, if not satisfactory for any reason, is simply written over by a new digitized image. The whole process requires less than a second and can be iterated in any manner. The digital image may then be processed and studied, or it may be moved to the next lower level of storage, the hard disk.

There is a variation on this method of digital image capture that is potentially very useful. It is sometimes desirable to capture two or more digital images that are, as nearly as possible, exactly registered in terms of scale, rotation, and translation (i.e., the images precisely overlay one another). This situation could arise, for example, if one wanted to perform the aforementioned blink comparison of images obtained at different times. Similarly, if certain processing operations involving the subtraction of one image from another, or the division of one image by another, are to be performed, registration of the images would be necessary.

In this case the procedure is as follows. When the desired scene is displayed in the live video format it is digitized into one image buffer (for example page 1); the second scene is then established on the live video and the two images, page 1 and input video, are sequentially displayed at moderately high frequency with

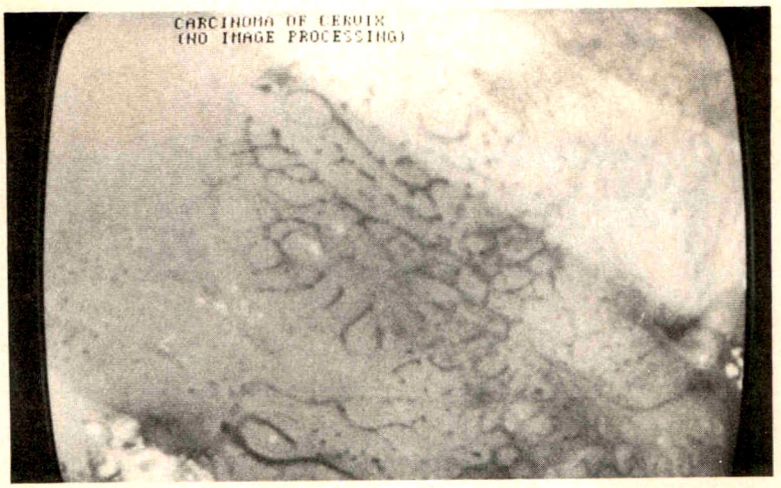


Fig. 1. Unprocessed image of cervix showing mosaicism surrounding the os.

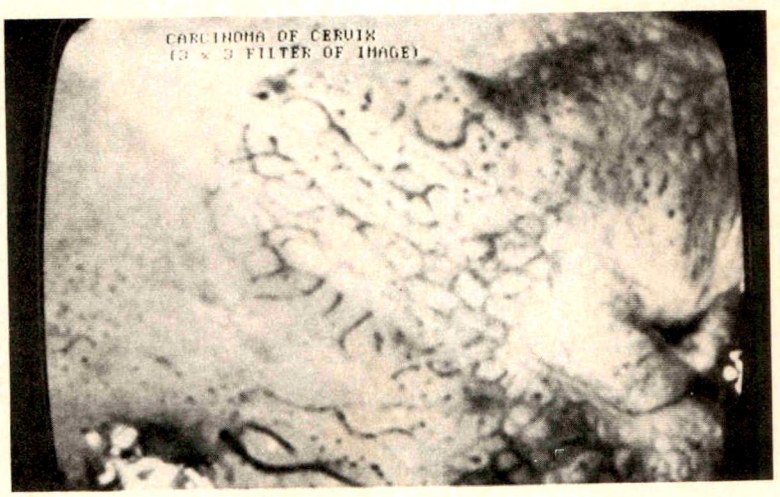


Fig. 2. The image of Fig. 1 processed by a pixel by pixel operation using a 3 × 3 digital filter convolution.

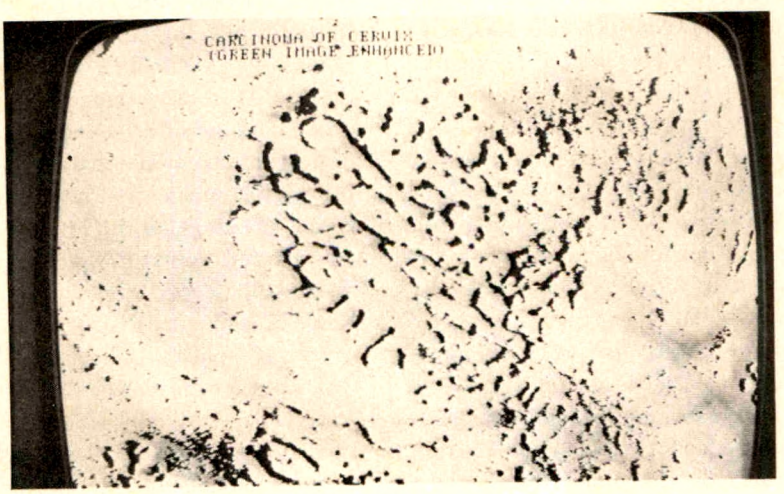


Fig. 3. The image of Fig. 1 showing enhancement of vasculature features with a digital filter operation comparing images obtained in white light and a monochromatic green band optical filter.

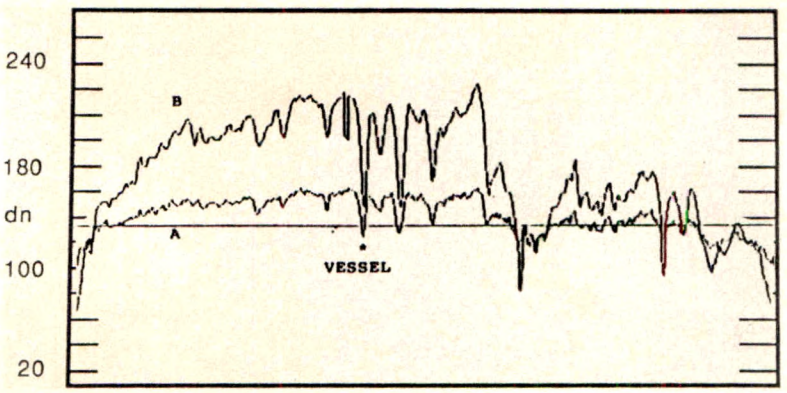


Fig. 4. A line plot across line 116 of the images in Figs. 1 and 2; *dn* is the data number value of the pixel. *Line A* is from the image before any processing; *line B* is from the same region after a 3 × 3 filter convolution process. The *asterisk* denotes a region of increased density corresponding to a blood vessel. Note the increased size of this peak relative to the background and the general decrease in intensity of the image (higher pixel values correspond to a whiter image).

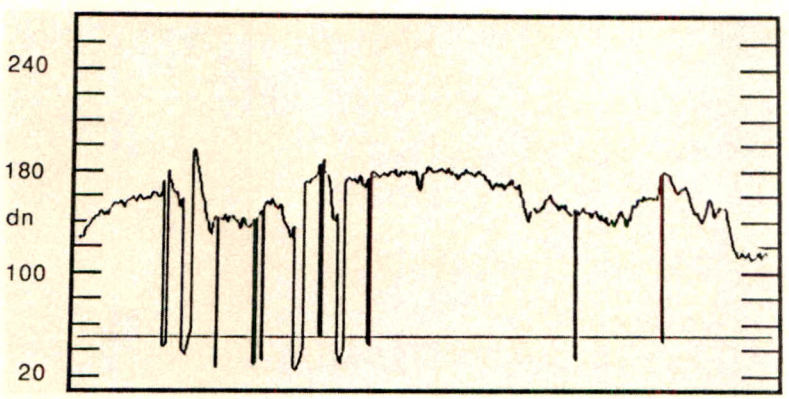


Fig. 5. Line plot through line 388 of the enhanced image shown in Fig. 1 with a pixel error of 15.

the blink comparison capability. Any errors in registration between the two images are readily apparent and easily corrected by moving the colposcope, thus changing the orientation of the live input image. When satisfactory registration between the two scenes is achieved the input image is then digitized as page 2. One possible use of this capability is to place an archived image from an earlier examination in page 1 and use the live image from the current examination as the second image for comparison.

For our current purposes we are interested in use of this capability to compare images obtained during the same examination but using different filtering operations during the examination.

From the standpoint of optical filter use, it is important to recall that light may be described as a wave phenomenon in which the nature of the light is defined by an amplitude and wavelength. Colposcopic examinations are often conducted with white light, which is the sum of electromagnetic energies over the range of wavelengths to which the eye is sensitive, typically blue at short wavelengths to red at longer wavelengths.

Specific colors, or narrow wavelength bands, of light may interact differently with different biologic tissues based on the energy in the light and the nature of the tissue. This phenomenon has been used to advantage in colposcopy, for example, by introduction of a green optical filter to enhance the contrast of blood vessels in the cervix. In fact, numerous filter combinations over a broad range of wavelengths could be implemented to provide potential enhancement of various tissues in colposcopic images. An interesting possibility involves taking advantage of the broad wavelength response of the charge-coupled device detector in the digital imaging colposcope, which has a significantly greater range of sensitivity than the human eye.

To accomplish this, we have begun experimentation with several different modes of filtering digital colposcopic images. These experiments include the use of (1) digital filters in the host computer, (2) optical filters in the colposcope optical path, and (3) combinations of both. In the following section we outline some examples of this type of work and suggest benefits and directions for future efforts.

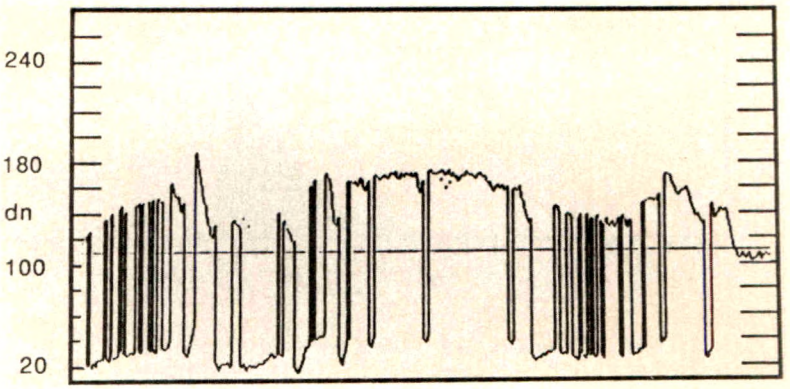


Fig. 6. The same as Fig. 5 but for a pixel error of 5 gray levels.

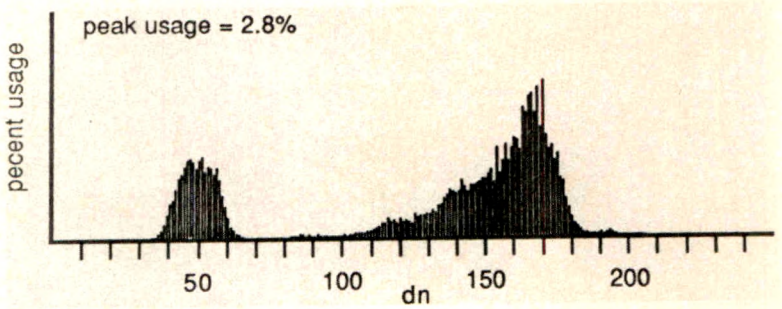


Fig. 7. The image histogram of the image produced by computer enhancement techniques described for Fig. 3; the pixel error threshold was set at 15 gray levels.

Results

One of the primary goals of the processing of colposcopic images is to accentuate the pattern of blood vessels of the cervix that is a feature diagnostic of cervical neoplasia. Two methods that are particulary useful and can be implemented on a microcomputer are the use of 3 × 3 digital filters, and the comparison of images digitized with and without green light illumination. The latter method is unique to colposcopy and the subject of a proprietary software algorithm of Western Reseach Company, Inc.

The 3 × 3 filtering of the image can be accomplished in about 10 seconds with software written in the C language. This is an adequate time but can be further accelerated by including machine language subroutines. The 3 × 3 filtering can produce excellent enhancement of visualization of the blood vessels. The background is deemphasized and the vessels are enhanced (for example, see Figs. 1 to 3). Fig. 4 shows a line plot through a region of vessels before and after filtering. The vessel feature is clearly emphasized; the area under the peak corresponding to the vessel is obviously greater in the filtered image while the baseline is greatly reduced.

A common feature of colposcopes is the presence of a green filter through which to observe the cervix. This light filtering system increases the contrast of the vessels although decreasing the overall light intensity of the image. We have designed an image processing algorithm to take advantage of the ability to obtain images with the green filter. This involves a pixel by pixel comparison of the green filter image with the normal white light image. Those pixels that are accentuated with the green filter are multiplied by a factor to emphasize those pixels. Since the entire green-filtered image has decreased intensity, compared with the white light image, it is necessary to correct for the average intensity of the images. The ability to differentiate features also depends on the average variance of individual pixel values. To correct for this problem it is necessary to determine the optimal difference between pixel values before a determination is made that the feature is truly darker in the green-filtered image.

The effect of setting the allowable variance in pixel values can be seen graphically in Figs. 5 and 6 that show line plots at the same level of the colpophotograph with different minimal intensity pixel difference criteria of 15 and 5 gray levels. The effect of increasing the criteria is to reduce noise because of random areas in which the green-filtered image is more intense than that of the white light–illuminated sample. This noise is seen as the sharp spikes. The specific areas of vessels are accentuated and are seen as smoother, broader regions of enhanced intensity. The effect can also be seen in

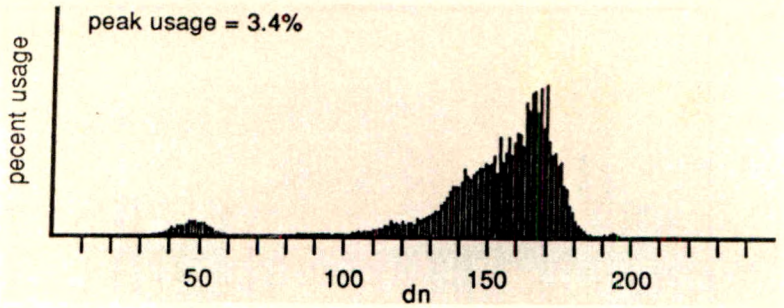


Fig. 8. The same as Fig. 7 but for the data in Fig. 6.

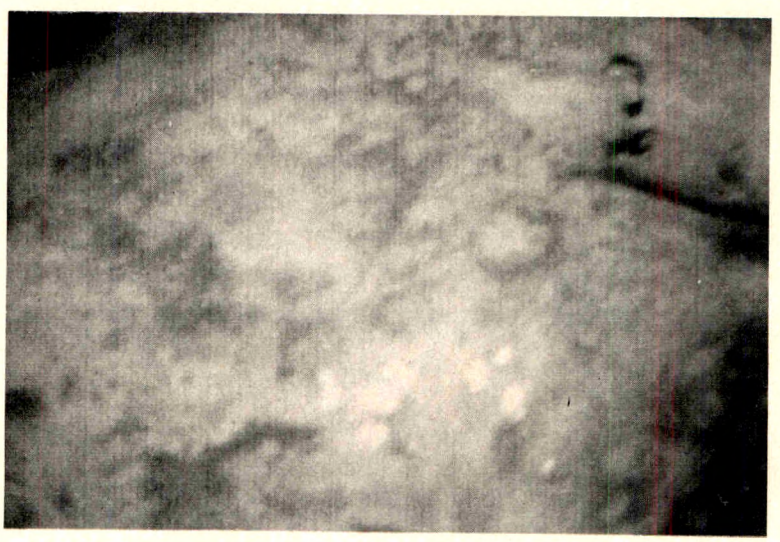


Fig. 9. A segment of an unfiltered colposcopic image obtained with the digital imaging colposcope.

the histograms of the entire image as shown in Figs. 7 and 8. The pixels corresponding to blood vessels are well separated as a new peak in the image histogram. With increasing stringency this peak is decreased in area as it becomes more specfific.

The result of this form of image processing can be seen most dramatically in Fig. 3, which is a photograph of the CRT display of the 256 gray level image of a colpophotograph of a cervical carcinoma. Compared with Fig. 1 there is a dramatic increase in intensity of the vessels. This type of enhancement may prove particulary useful in the development of algorithms for automatic extraction of vascular features in colposcopic images.

Another approach to filtering of colposcopic images that may offer benefits in understanding the nature and condition of the tissue under examination is the use of multispectral imaging. The concept here, the same as is widely used in remote sensing, involves imaging the same area of the cervix in light that is limited by two or more different wavelength bandpasses (i.e., different colors). The resulting images must be exactly registered, as described in the method discussion, and the resulting multispectral images may then be subtracted from one another, or one may be divided by the other. The result is the selective enhancement of features that respond differently to the specific wavelengths of light used. A more detailed discussion of elements of color and multispectral colposcopic imaging may be found in Craine et al.[6] and Craine et al.[7]

In our preliminary experiments we have worked with broadband filters isolating violet, green, yellow, orange, and red light. The images in each band have been registered and various combinations of subtracting and dividing the images have been tested. An example of a segment of an unfiltered image is shown in Fig. 9; the green image divided by the corresponding red image is shown in Fig. 10. It is apparent that selective contrast enhancement has taken place and that portions of the tissue have been emphasized.

Comment

The computerized digital imaging colposcope allows for storage of the image, serial observations and analysis of the lesion, accurate measurement of the lesion, enhancement and manipulation of the digital image, and the use of a variety of optical filters to create new, potentially useful versions of the image. The enhanced

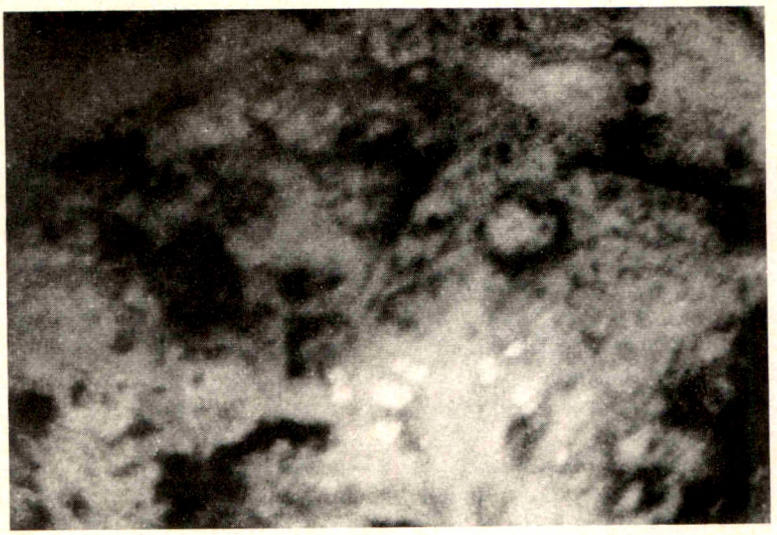


Fig. 10. The same scene as in Fig. 9 but resulting from the division of the green filtered image by the corresponding red image.

colposcopic image, analyzed with any or all of the aforementioned options, then becomes useful as a research tool to fully assess the surface structure of the uterine cervix.

In addition to the generally recognized advantages of digital imaging, the digital imaging colposcope we have described offers a number of novel features that make it attractive for use in a variety of research programs; many of these features may eventually prove to be clinically useful.

The preliminary work we report here clearly indicates that we can accomplish the following: (1) colposcopic images can be enhanced with digital filters as well as the traditional green optical filter, (2) multiple colposcopic images can be registered using the dual-frame buffer capability of the system, and, (3) multispectral colposcopic images can quickly and easily be compared with image subtract and divide functions.

Our plan is to use these capabilities to build a substantial database of digital colposcopic images that represent a range of heretofore unobtainable colposcopic views of the cervix. These images will be analyzed in the context of histopathology with a goal being the development of a potentially new, dynamic colposcopic methodology.

We appreciate the cooperation and assistance of Samaritan Medical Center of Phoenix, Arizona in ongoing research on this methodology. Valuable assistance was provided by Dr. John R. Engel and Neil T. Wemple.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Edward C. Hill, San Francisco, California. Last month we were privileged to view the surface of the planet, Neptune, by way of computer-enhanced images transmitted from a video camera two billion miles away. This month, in a similar fashion, we are given the opportunity to study a surface much more familiar to us, the cervical mucosa, seen through the colposcope and transmitted to a microcomputer via a cable 5 to 7 meters long. Although the significance of the information transmitted back to earth from the satellite *Voyager II* has been pronounced by space experts as equal to that of the discovery of America by Christopher Columbus, we do not yet know where this novel use of a computerized digital imaging colposcope will lead. Dr. Crisp and his coworkers in this endeavor, Drs. Brian and Eric Craine, have followed the lead of a number of Italian investigators in combining the colposcope with computer graphics. This is only a milestone on the road of attempts to enhance colposcopic images. Dr. Crisp mentioned that the basic optical system of the colposcope has not changed since it was introduced by Hinselmann in 1925. Actually, there have been improvements in

illumination, magnification, and lengthening of the focal distance from 12 to 20 cm. In 1938, Hinselmann described the effect of dilute acetic acid on the appearance of the mucosa, enhancing the visualization of columnar epithelium, transformation zones, and atypical epithelium. The introduction of the green filter by Kraatz in 1939 was a great step forward because it facilitated the visualization under white light of the vascular pattern of the mucosa.

The problem of properly recording colposcopic observations was recognized very early, and it was soon acknowledged that this could be accomplished only through colpophotography. Both color and black-and-white photography have been used, and each has its advantages and disadvantages. In my discussion I would like to pay tribute to the contributions of two Norwegian pioneers of this method, Dr. Odmund Koller, and his successor, Dr. Per Kolstad, of the Norwegian Radium Hospital in Oslo, who have used black-and-white photography to great advantage in advancing our knowledge of the microangioarchitecture of the cervix in health and in disease. Their technique certainly was one of the most significant in the various attempts over the years to enhance and record colposcopic images, the subject of this article.

Twenty-five years ago, while spending part of a sabbatical year in Stockholm, Sweden, I met a young Norwegian gynecologist, Dr. Kolstad, who at that time was pursuing his work in colposcopy at the Karolinska Institute. He used a technique of colpophotography developed by Dr. Koller. To my knowledge, this method was the first attempt to show, record, classify and correlate the vascular patterns of the cervix with various clinical entities, particulary those associated with neoplasia. The method involved a high-resolution optical and photography system, using ultrafine grain black-and-white film with orthochromatic sensitivity, strong illumination, and a high magnification. These were achieved by shortening the focal length to 12.5 cm (rather than the 20 to 30 cm length used in routine colposcopy); this required a special vaginal speculum. The magnification objective on the Zeiss colposcope was set at $\times 16$, and the camera lens aperture at f/32. This combination resulted in a resolved distance of 15 μm and a depth of field of 0.8 mm. To obtain complete pictures of the entire portio vaginalis, up to 30 exposures were made. These were then enlarged five times, the best prints were selected and arranged into composite pictures mounted on poster board.

The advent of portable television cameras allowed the attachment of these recording devices to the colposcope, and with the adaptation of the television monitor to the computer, it was inevitable that there would eventually be a marriage between the colposcope and computer graphics. But is this just another example of technology looking for an application? Contini and his coworkers in Milan have already published their work in this area in the March 1989 issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY (see the authors' ref. 5), describing it as a new method that may be useful not only for documentation but as a research tool. It is fascinating to see what the authors have been able to accomplish in enhancing various colposcopic findings through digital manipulation of the images. Because of the price tag of about $25,000 in addition to the cost of the colposcope, it is highly unlikely that the average gynecologist will acquire one. Speaking from a position of having tried over a period of several years in the 1960s to follow the natural history of cervical dysplasia with a combination of cytology and colpophotography, I can readily appreciate the facility that this method allows. It has the advantages of the ability to correct recording techniques "on the spot," of the enhancement features that are available, and most importantly, of the ability to store, retrieve, and compare images over time. With the use of a modem, colposcopic images can be transmitted via telephone lines cross country or even abroad. Clearly this new method is worth pursuing.

DR. CRISP (Closing). Thank you, Dr. Hill, for your comments. I visited Dr. Contini's clinic in Milan 2 years ago and was aware of their recently published data utilizing the computer to store and compare colposcopic images. Our instrument adds, for the first time, the ability to use light filters from four different color sources to provide combinations of lights of different wavelengths. We lack any real knowledge of which tissues best absorb which type(s) of light. Light is an electromagnetic force that varies in amplitude and in wavelength from red to blue. It is my impression that different disease states of the cervix absorb different colors of light. Therefore this extension of the use of a green filter that we have discussed will add to the clinician's ability to categorize cervical lesions in the range from benign to malignant.

The application of computer technology gives the colposcope a new dynamic ability to apply different combinations of light filters to the study of cervical neoplasia. This use of various types and combinations of light energy will hasten the development of photobiology.

TRANSACTIONS OF THE FIFTY-SEVENTH ANNUAL MEETING OF THE CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

Men without chests

Presidential address

James H. Maxwell, MD
Colorado Springs, Colorado

In coming before the body of the Central Association of Obstetricians and Gynecologists this morning, I am discharging the most difficult of the responsibilities that are charged to the president of the organization, that of addressing the Association about some matter that is important in our field, and of doing that with integrity and sensitivity. The subject I have chosen to speak about has to do with decision making. As I hope will be clear as the speech unfolds, I consider actions derived from decision making the most important single problem facing the body of medicine in the United States today. The magnitude of the problem is definitely not limited to the practice of medicine, but I will confine my remarks to that field.

Until quite modern times, almost all persons believed the universe to be such that there was a congruence of our nature, our feelings, and the universe wherein we live. An excellent example of this congruence is expressed in the second paragraph of the Declaration of Independence of the United States of America, where it is stated, "We hold these truths to be self-evident that all men are created equal, that they are endowed by their creator with certain unalienable rights. Among these are life, liberty, and the pursuit of happiness. . . ."

In the early years of the last century, with the introduction of Hegel's system of philosophy, which incorporates the thesis-antithesis-synthesis concept, relativism was born. The fruit of relativism is a general philosophic theory that all values are subjective and trivial. In our day this has worked out by the fluidity of the law, with the interpretation and the reinterpretation of the Constitution, to mean whatever the *zeitgeist* or spirit of the time deems it to be. The judges of ancient Israel expressed the same thought, "Every man did what was right in his own eyes." There was no rock-solid standard applied and behavior flowed up or down as the moral climate of each day dictated.

Even Hegel and his pupils recognized the need of some "absolute" or ultimate source of authority, and he determined that the state held ultimate authority. The world of our fathers and ourselves has suffered through two great world wars and their aftermaths, the awful holocaust, and Vietnam because Hegel taught that the *state* was the ultimate arbiter of values. Marx used Hegelian philosophy as the value basis of communism. Hitler took Hegel through Nietzsche and formed the concept of the super race; thereby these two have subjected the modern world to the most terrible brutality known to mankind.

Unfortunately, these same concepts of relativism have essentially totally infiltrated the fields of the social sciences and the field of education. For confirmation, meditate on what Alan Bloom was really saying in *The Closing of the American Mind.*

Much was made in the early days of the twentieth century of Einstein's theory of general relativity in which a direct relationship between mass and energy was postulated. The idea of relativity was quickly (and erroneously) applied to a relativistic value system and was deemed to have scientifically proved at most, and supported at least, the relativistic position of the social and political scientists. Lost to the eyes of the relativistic position was the powerful fact that the relationship of mass and energy, expressed in the general theory of relativity, was bound by the strongest of all absolutes in the physical world—the speed of light—

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unchanging, unalterable, solid as a rock, not changing with the mood of the current leading physicists.[1]

Now what does all of the foregoing have to do with obstetricians and gynecologists in the Central Association? Much, I do believe. This past spring a great festival was held in Denver to honor one of our own—Tommy Evans, emeritus professor at Colorado University and former president of both the Central Association and the American College of Obstetricians and Gynecologists.

The most enthusiastic participants in this festschrift for Tommy were many of his former students. Why were they there? To honor *The Professor.* What had The Professor taught them? Lots of facts about our discipline; when to induce labor and when not to, the best therapy for endometriosis, an effective algorithm for the management of infertility, and on and on. But in talking with many of the students, some of whom are now professors in their own right, what The Professor had taught them was an approach to decision making.

To make good obstetric and gynecologic decisions requires the application of good science and good ethics to a problem. All of us realize that science changes as learning unfolds. For example, many of us in this audience learned in our generation in our genetic course in college that there were 48 human chromosomes. Now all of this has changed, and molecular biology is delving deeply into the very life processes. The entire process of continuing medical education, which is the very cause for the existence of the Central, as well as the peer-review medical journals, is dedicated to supplying the latest and best of science and learning.

But what of the ethics? To mire ethics in the morass of relativism completely strips our values of any firm basis for excellence. Ethics requires "the constant," just as much as the general theory of relativity required "the constant." The denial of this need for "the constant" subjects humanity to the control of either the trousered apes who make all decisions by visceral reaction, or to the cerebral guides who place no value on any other than that which their minds conceive. Our need is for men with chests—decision makers who integrate visceral response and cerebral acumen with "heart," ethics that do not fluctuate with the whim or need of the moment, integration of right and courage.[2]

Values that are based on "the constant," and behavior that is derived from these values is good and right. It is right not because someone forces it on us, but rather, it stands as right on its own. It is right because it fits. It is right because it is congruent with "the constant." When we have a value system based on relativism, questions arise in the minds of everyone, such as, does that mean that we can decide for ourselves if we will be honest or not? Is it better to tell a lie when it appears to be in our best interest rather than to always be honest? The same kind of ethical quagmire exists when one looks at any question of behavior from a relativistic viewpoint. One of the great ironies of our day is, that we laud the value. We say "honesty is the best policy," but our behavior teaches the learner the exact opposite. The learner sees, in relativistic behavior, a self-seeking value as the only value; and this of course leads to moral anarchy. As C. S. Lewis said, "We continue to clamor for those very qualities we are rendering impossible . . . we make men without chests and expect of them virtue and enterprise. We laugh at honor and are shocked to find traitors in our midst. We castrate and bid the geldings be fruitful."[3]

Is this a new idea? Not at all. Aristotle taught that the aim of education is to make the pupil like and dislike what he ought.[4] In *The Republic* Plato stated that the well-nurtured youth is one "who would see most clearly whatever was amiss in ill-made works of man or ill-grown works of nature, and with a just distaste would blame and hate the ugly even from his earliest years and would give delighted praise to beauty, receiving it into his soul and being nourished by it so that he becomes a man of gentle heart. All this before he is of an age to reason; so that when reason, at length, comes to him, then, bred as he has been, he will hold out his hands and welcome and recognize her because of the affinity he bears to her."[5] In early Hinduism, that conduct in man that can be called good consists in conformity with or almost participation in the *Rta*—that great ritual or pattern of nature and supernature that is revealed alike in the cosmic order, the moral virtues, and the ceremonial of the temple. Righteousness, correctness, order—the *Rta*—is constantly identified with sayta or truth, correspondence with reality.[5]

The Chinese also speak of a great thing (the greatest thing) called the Tao. It is the reality beyond all predicates, the abyss that was before the creator himself. It is nature. It is the way. The road. It is the way in which the universe goes on. The way in which things everlastingly emerge, stilly and tranquilly, into space and time. It is also the way in which every man should tread in imitation of that cosmic and supercosmic progression, conforming all activities to that great example. "In ritual," say the Chinese, "it is harmony with nature that is prized."[6]

Likewise, the ancient Jewish tradition praised the law as being "true." The Indian sources emphasize truth as "correspondence," whereas the Judaic emphasis is rather on the reliability or trustworthiness of the truth. Faithfulness and permanence are other orders that could be alternative renderings. Truth is that which does not deceive, which does not give, which does not change. It holds water.[7]

There obviously are many differences in these various cultural backgrounds, but all that which is common

with that which is within the Tao is something we should not neglect. It is the doctrine of objective value, the belief that certain attitudes are really true and others are really false to the kind of things the universe is and the kind of things we are. Such a philosophy of life demands a response from us that is congruent, that is, in harmony with this world view.

All of us have watched as young practitioners of our art have come on the scene. We have observed some of true integrity, and we have also observed some whose decisions have been truly the decisions of trousered apes, being driven only by avarice or personal gain. This is not limited to our younger colleagues. We have seen more mature practitioners stumble when faced with moral dilemma. The problems of identifying and detecting those who practice such deception is indeed a difficult one, fraught with many problems in our litigious society. But that should be no obstacle or deterrent to the profession identifying and culling out those who are not worthy of the almost sacred charge of the health and care, not only of women, but of the next generation—the unborn.

Obviously, a heavy responsibility falls on the shoulders of the professors. They are the ones who are in contact with the physicians in training, both at the doctoral level and at the specialty-training level. These persons need great wisdom and great support in the task they face of training, not only in the field of the science, which in a sense is the easy part, but also in the field of the ethic. It would be far better were all candidates for the doctoral degree to be fully screened and fully evaluated and all be of high ethical and moral practice; however, we would be naive to perceive the reality of the situation thusly. Therefore, it is incumbent on the members of the profession as a whole to formulate strategy for the detection and self-discipline of unethical behavior.

It is totally unrealistic to put the burden of moral behavior totally on the shoulders of the professor. It is incumbent on all persons who bear the name of obstetrician and gynecologist to look out for the welfare of our patients. First, foremost, and essentially exclusively, we must back and support the professor in the initial processes of both teaching and weeding out. But we also, in our day-to-day exposure to our colleagues and to the rest of the health care team, must practice and expect of our peers, ethical behavior of the highest order. We cannot expect ethical behavior based on "the constant" from our peers and practice relativistic ethics ourselves. This indeed would be nothing short of castrating the stallion and bidding the gelding be fruitful. The relativist who expunges "the constant," who lives without the Tao, has indeed produced an ethical system that is totally devoid of any life force.

The goal of this idea is not good ethics per se, but rather, good ethical behavior. One of the saddest features of human existence is the disparity between what one thinks he believes, or what one states he believes, and what one actually does believe. The mark of the man who is truly within the Tao, the mark of the man of true integrity, the mark of the man who is in congruence with his belief is the behavior of such a man when such behavior does not appear to be in his "best interests" but is in harmony with his ethics. This man is no trousered ape, responding only to the basest of human drives, nor is this man the cerebral leader who has no comprehension of or sensitivity to his fellow man. Rather, this is the man of integrated personality and character. This indeed is a man with a chest, a person who has a basis in objective reality for decision making, a man with the courage to apply that objective reality to his own life and to the most difficult of situations that he faces day by day in his pursuit of the goal of excellence in the care of women and their unborn. This then is a call to dedicate ourselves to this goal. Let us not be "men without chests."

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A prospective controlled study of outcome after trauma during pregnancy

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In a prospective cohort study, 85 women who suffered varying degrees of trauma during pregnancy (12 to 41 weeks) were compared with a control group of pregnant women matched for gestational age. Fetomaternal transfusion occurred significantly more frequently in the study group (30.6% vs 8.2%, $p < 0.05$). Study subjects whose placentas were anteriorly placed were at increased risk for fetomaternal transfusion on comparison with other placental positions (47% vs 23.5%, $p < 0.05$). Immediate adverse outcomes including abruptio placentae occurred frequently in the study group (9.4%) and were *not* predictable on the basis of injury severity. When immediate adverse outcomes were excluded, there was no difference in pregnancy outcome. Four hours of cardiotocographic monitoring used as a screening tool was found to be an extremely sensitive but nonspecific indicator of immediate adverse outcomes. On the basis of these findings, it is recommended that routine screening for fetomaternal transfusion occur in all pregnant women who suffer trauma during pregnancy beyond 11 weeks' gestation and that a minimum of 4 hours of cardiotocographic monitoring occur in women >20 weeks' gestation. (Am J Obstet Gynecol 1990;162:1502-10.)

Key words: Abruptio placentae, pregnancy, injury, pregnancy outcome, fetomaternal hemorrhage

Trauma during pregnancy is associated with an increased risk of spontaneous abortion, preterm labor, abruptio placentae, fetomaternal transfusion, and stillbirth.[1-9] The frequency and time of onset of these complications are not clear and may be related to the type of injury, location of injury, gestational age, or severity of injury. This uncertainty has prompted a variety of recommendations for the management of the pregnant patient who has suffered trauma.[10-13]

This cohort study was designed to prospectively evaluate pregnant women who have suffered trauma during pregnancy, with uninjured pregnant women serving as controls. Acute complications (i.e., abruptio placentae, fetal death, rupture of membranes, onset of labor, preterm delivery), and the incidence and volume of fetomaternal transfusion, as well as pregnancy outcome, are compared.

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Material and methods

From November 1985 to August 1988, 85 women presenting to William Beaumont Hospital with a complaint of trauma during pregnancy were enrolled. Subjects were included if they sustained any severity of trauma at or beyond 12 weeks' gestation. Patients with isolated distal extremity injuries were excluded. Each subject was first evaluated in the Emergency Department, and after stabilization, those patients at or beyond 20 weeks' gestation were transferred to the labor and delivery suite for a minimum of 4 hours of cardiotocographic monitoring (model 8040A; Hewlett-Packard, Palo Alto). In many cases monitoring was begun in the Emergency Department. Subjects at or beyond 20 weeks' gestation also had a complete ultrasonographic examination performed (biparietal diameter, abdominal circumference, femur length, amniotic fluid volume, placental location, cerebral ventricular diameter, and calculated estimated fetal weight). Patients <20 weeks' gestation with absent fetal heart tones, abdominal pain, or vaginal bleeding underwent a similar ultrasonographic examination. The retroplacental area was carefully evaluated in all patients for findings suggestive of abruptio placentae.

Historical information included the type of injury: motor vehicle accident, fall to horizontal, fall from height, or direct blow to the abdomen (kick, punch). If

the subject was involved in a motor vehicle accident, the restraint system used (if any), speed of the vehicle, damage to the vehicle, and patient position in the vehicle were recorded if possible. The time from injury to presentation was noted as were any symptoms or complaints on admission. A thorough physical examination and appropriate roentgenography or other diagnostic studies (e.g., peritoneal lavage) were performed as indicated.

Cardiotocographic monitoring of all study patients >20 weeks' gestation was performed for a minimum of 4 hours. The 4-hour monitoring record was evaluated for uterine contractions, baseline fetal heart rate, periodic changes, and overall assessment of fetal well-being by a single investigator who was blinded to outcome (R. P. L.). Subjects were categorized into one of five groups on the basis of the frequency of uterine contractions. Those not having contractions were identified as group 0, those with fewer than one contraction every 15 minutes were placed in group I, patients with contractions every 10 to 15 minutes were placed in group II, those with contractions every 5 to 9 minutes were put in group III, and those with contractions every 2 to 5 minutes were placed in group IV.

A control group matched for gestational age (±1 week) was selected from a large group of patients presenting to the Department of Fetal Imaging for obstetric ultrasonography. Subjects were also selected on the basis of the likelihood of obtaining complete follow-up (i.e., delivery at William Beaumont Hospital). The only exclusion criterion was a history of recent vaginal bleeding (within 1 month).

Both groups had an acid elution (Kleihauer-Betke) assay performed at the time of entry into the study. The method used has been previously described.[14] A minimum of 1000 cells were counted. The estimated volume of fetomaternal transfusion was based on the number of fetal cells seen on the smear and an estimate of maternal blood volume. Apgar score, birth weight, gestational age at delivery, and length of neonatal stay were recorded. Subjects who were delivered outside of the institution were contacted by telephone and their records reviewed for outcome.

All data were analyzed with the SAS package. Discrete variables were compared by χ^2 analysis. The two-tailed Student t test was used for continuous variables, and the Fisher exact test was used when appropriate. A p value ≤ 0.05 was considered to be statistically significant.

The study was approved by the Human Investigation Committee at William Beaumont Hospital, and appropriate consent forms were signed by each subject. Eight trauma subjects who were eligible refused admission into the study.

Table I. Demographics

	Trauma (n = 85)	*Control (n = 85)*
Age, yr (mean, range)	27.1 (17-41)	28.4 (19-39)
Gravidity (mean, range)	2.5 (1-7)	2.3 (1-6)
Parity (mean, range)	1.0 (0-6)	1.1 (0-5)
Gestational age at entry, wk (mean, range)	29.3 (12-42)	29.1 (12-41)

There was no significant difference between the two groups.

Results

A total of 170 women were enrolled in the study (85 trauma subjects and 85 controls). Outcomes were available for all pregnancies. The age, gravidity, parity, and gestational age at the time of entry are listed in Table I. Prior preterm deliveries were also noted. There was no significant difference between the two groups for any of these variables.

Injury type and severity. Motor vehicle accidents were the most frequent cause of trauma (n = 51; 60%), followed by falls (n = 22; 25.9%) and direct blow to the abdomen (n = 12; 14.1%). Falls were categorized as either fall to horizontal (n = 12) or fall from height (n = 10). Thirty-nine patients involved in motor vehicle accidents were restrained (76.5%), with one exception all subjects were in three-point restraint. Thirty-seven women were drivers of the vehicle, 12 were front-seat passengers, and two were rear-seat passengers. The severity of the motor vehicle accident ranged from minor car damage with no demonstrable maternal injury to extensive vehicle damage and critical illness of the victim at presentation (e.g., hemorrhagic shock, comatose from traumatic brain injury, multiple organ system involvement). Of all trauma victims, 75 (88.2%) had minor or no injuries on clinical examination (minor bruising, lacerations, contusions), 8 (9.4%) had moderate injuries (broken long bones, fractured ribs, extensive bruising), and 2 (2.4%) were critically ill at presentation.

Immediate adverse outcomes. Immediate adverse outcomes were prospectively defined as either abruptio placentae within 72 hours of injury, rupture of membranes within 4 hours of injury, onset of labor within 4 hours of injury that resulted in delivery during the index hospitalization, or fetal death within 7 days of the traumatic event. Table II lists all immediate adverse outcomes along with injury severity. Although both critically injured women suffered abruptio placentae, immediate adverse outcomes occurred more frequently among those less severely injured, as three of the five subjects who suffered abruptio placentae occurred in

Table II. Immediate adverse outcome

Injury severity	*n*	*Abruptio placentae*	*Ruptured membranes*	*Fetal death*	*Delivered (total)*
Minor	75	3	1*	0	5†
Moderate	8	0	1	0	1
Severe	2	2	2*	1‡	2
TOTAL	85	5 (5.9%)	4 (4.7%)	1 (1.2%)	8 (9.4%)

*Rupture of membranes occurred in addition to abruptio placentae.

†Includes two patients who were delivered without evidence of abruptio placentae.

‡Fetal death resulted from complete abruptio placentae.

Table III. Outcome of pregnancies complicated by abruptio placentae (all delivered during index hospitalization)

Patient No.	*Fetal monitor tracing*	*Apgar score*		*Venous cord pH*
		1 min	*5 min*	
1	Persistent type II decelerations	3	6	7.03
2	Tachycardia	5	8	7.16
3	Persistent type II decelerations; tachycardia	4	8	7.13
4	Deep variable decelerations; tachycardia	8	9	7.26
5	No fetal heart tones	0	0	Not performed

the minor injury group. Two of these women had entirely normal results at physical examination on admission.

Of the pregnancies that were complicated by abruptio placentae, all ended with delivery during the index hospitalization. One of the fetuses was dead on presentation as a result of a complete abruptio placentae, and the remaining four were delivered urgently by cesarean section because of abnormal fetal heart tracings. The outcomes of all pregnancies complicated by abruptio placentae are shown in Table III.

Three patients without evidence of abruptio placentae developed labor during the index hospitalization that resulted in delivery. These pregnancies were at 36, 38, and 41 weeks' gestation. No neonatal morbidity or mortality resulted from these pregnancies.

Fetomaternal transfusion. The rate of fetomaternal transfusion was 26 of 85 in the trauma group compared with 7 of 85 in the control group (30.6% vs 8.2%, $p = 0.0001$). The mean estimated volume of transfusion was 12.2 ml (range 5 to 69 ml) in the study group compared with 3.2 ml (range 2 to 8 ml) in the control group ($p = 0.02$).

In comparison with other placental locations in the trauma group anterior placental site was more frequently associated with fetomaternal transfusion (47% vs 23.5%, $p < 0.05$). There was no similar association in the control group. The physical finding of uterine tenderness also was more frequently associated with fetomaternal transfusion in comparison with absence of this finding (65% vs 32%, $p < 0.05$). No other physical finding was associated with fetomaternal transfusion. Trauma subjects who were restrained during motor vehicle accidents had a tendency to fetomaternal transfusion on comparison with those not restrained, but this difference did not reach statistical significance ($p = 0.06$). There was no definite relationship between uterine activity, fetal heart tracing abnormalities, and the risk of fetomaternal transfusion. None of the subjects demonstrated a sinusoidal fetal heart rate pattern.

The pregnancy complicated by the largest fetomaternal transfusion (69 ml) was terminated shortly after the accident because of fetal distress associated with abruptio placentae. The cord hematocrit was 36% and the neonate required transfusion after delivery. No other complications directly attributable to fetomaternal transfusion were noted. All Rho (D)–negative women who had fetomaternal transfusion were treated with Rh immune globulin in the appropriate dosage.

Pregnancy outcome. Birth weight, 1- and 5-minute Apgar scores, gestational age at delivery, type of delivery, and neonatal length of stay in both groups, excluding those subjects with immediate adverse outcomes, are shown in Table IV. When immediate adverse outcomes and their controls were excluded, there was no difference in any of the variables between the two groups.

Cardiotocographic monitoring and ultrasonography. All subjects >20 weeks' gestation were monitored for a minimum of 4 hours after the traumatic event ($n = 60$). Only four of the 60 subjects had essentially no uterine activity during the 4-hour monitoring period (6.7%). Fig. 1 illustrates the uterine activity among all contracting patients. Nearly two thirds of the subjects were having contractions at a frequency of every 2 to 5 minutes during the first hour of monitoring (group IV). The size of this group decreased progressively over the 4 hours, at which time only 28.6% of women were having contractions at that frequency. Conversely, 19.6% of women were having contractions at an interval greater than once in 15 minutes (group I) during the first hour, and this group increased in size over time to include a total of 37.5% of all subjects at the 4-hour mark. Groups II (contractions every 6 to 10 minutes) and III (contractions every 11 to 15 minutes) increased slightly over time at the expense of group IV.

All women who had immediate adverse outcomes (except one patient with only rupture of the membranes) were in group IV at some point during the 4 hours of monitoring. One woman who had a clinical apparent abruptio placentae 6 hours after the traumatic event began in group I at hours 1 and 2 and progressed to group IV at hours 3 to 6, at which time she had vaginal bleeding and eventually revealed persistent late decelerations of the fetus necessitating urgent operative delivery.

The use of tocolytic drugs was generally discouraged, but one patient was treated with parenteral ritodrine; she was seen at 28 weeks' gestation with contractions every 2 to 5 minutes after a motor vehicle accident. The frequency of uterine activity decreased over the next 45 minutes. The medication was discontinued after 90 minutes as chest pain developed. No other tocolytic therapy was begun, and contractions stopped spontaneously over the next 180 minutes. She was admitted for a total of 44 hours and was discharged without medication. She was delivered of a healthy 3.42 kg male infant at 39 weeks.

All subjects who were in groups II, III, or IV at any time during the 4-hour monitoring period were admitted beyond 4 hours (for a minimum of 24 hours). Subjects in group 0 or I during the entire 4-hour monitoring period were discharged at the end of the 4 hours unless uterine tenderness, a nonreassuring fetal monitor strip, vaginal bleeding, rupture of the membranes, or any serious maternal injury was present. Of the 60 women eligible for admission (>20 weeks' gestation), 42 were admitted beyond the 4-hour period (70%). All patients discharged at the end of the 4 hours or at 24 hours had a live birth. Gestational age at delivery, Apgar score, and birth weight were similar to those of the matched control group in all discharged patients. In patients admitted beyond the 24 hours, there was one fetal death (2.4%) and seven other deliveries (16.7%).

Ultrasonography predicted abruptio placentae in two of five patients (40%), but both of these patients had a clinically evolving abruptio placentae (vaginal bleeding and frequent uterine activity) at the time of the ultrasound. In three patients who did suffer abruptio placentae, the admitting sonogram did not suggest the diagnosis.

Comment

The management of trauma during pregnancy has evolved from a variety of protocols developed in nonpregnant trauma victims. Although these principals generally translate in very serious injuries, the less seriously injured pregnant woman is more problematic. The protocol developed herein was able to predict the major fetal morbidity experienced in this study. Interestingly, in the women who did not suffer immediate adverse outcomes, the accident appears to have had a minimal, if any, impact on pregnancy outcome in terms of birth weight, gestational age at delivery, or Apgar score. This finding is important to allay the fears of both the obstetrician and the pregnant woman after she is discharged home following the monitoring period. Nonetheless, it is important to instruct the patient to return if any signs or symptoms of preterm labor or abruptio placentae do occur after discharge, as the apparently rare episode of delayed abruptio placentae has been described.[15]

Several studies have noted that the incidence of abruptio placentae after major automobile accidents varied between 6% and 35%, but most of these series involve women who have suffered major injuries.[2, 3, 12] In this series, which involved mostly minor trauma, the incidence of abruptio placentae was 5.9% (4.0% in the minor injury group). Importantly, it appears that even relatively minor deformation forces are sufficient to shear the placental attachments away from the decidua basalis. It is clear that neither physical findings nor the severity of injury is able to rule out immediate adverse outcomes. Routine cardiotocographic monitoring for a minimum of 4 hours appears to be very sensitive for predicting immediate adverse outcomes including abruptio placentae. Ultrasonography does not appear to be particularly useful in predicting abruptio placentae after trauma (sensitivity = 40%). Nonetheless, ultrasonography may still be useful in these patients for other reasons (estimating fetal weight and gestational age, biophysical profile, amniotic fluid volume).

The current protocol recommended that tocolysis not be attempted, although the ultimate decision was left to the attending physician. Of the 35 women who were having frequent contractions during the monitoring period (group IV, 2 to 5 minutes apart), five subsequently suffered an abruptio placentae requiring delivery, and three others were delivered of their infants during the index hospitalization (at 36, 38, and 41 weeks). Tocolysis was discouraged as it was felt that regular uterine activity after trauma was a result of abruptio placentae until proved otherwise. This hypothesis was mostly borne out during the study because five of the eight patients who were delivered did suffer an abruptio placentae. In those women with frequent contractions, contractions stopped in 90% without tocolysis. Of those patients who were delivered during the index hospitalization without evidence of abruptio placentae, all were at or near term, and no serious fetal morbidity resulted from these deliveries. Uterine activity after trauma may result from a uterine "contusion" resulting in extravasation of blood from myometrial capillaries and subsequent irritability. As this extravasated blood is resorbed, the uterine irritability diminishes. We feel that the initial presentation of

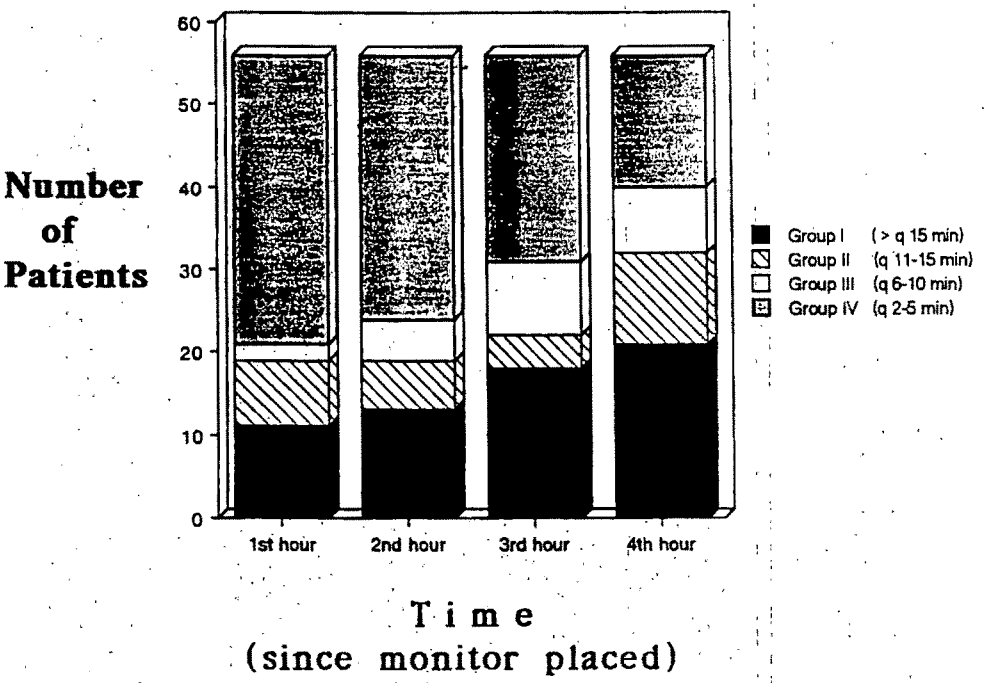


Fig. 1. Number of patients with uterine contractions at various frequencies during the first 4 hours of monitoring ($N = 56$).

Table IV. Pregnancy outcome (excluding immediate adverse outcomes)

	Trauma	*Study*
Birth weight (kg, mean ± SD)	3.44 ± 0.58	3.53 ± 0.57
Gestational age at delivery (wk, mean ± SD)	38.9 ± 4.5	39.8 ± 2.2
Apgar score		
1 min	7.5	7.7
5 min	8.8	8.9
Delivery type (% cesarean section)	21	24
Neonatal length of stay (days ± SD)	4.1 ± 4.0	4.1 ± 6.8

There was no significant difference for any variable between the two groups.

abruptio placentae and "contusion" are indistinguishable and tocolysis should not be attempted.

Pregnant patients who suffer trauma are clearly at risk for fetomaternal transfusion; this finding confirms an earlier report by Rose et al.[5] Neither the severity of injury nor the presence of uterine activity was predictive of fetomaternal transfusion, although an anteriorly positioned placenta and the presence of uterine tenderness did place patients at increased risk. With one exception, patients with fetomaternal transfusion experienced no difference in pregnancy outcome on comparison with controls. This contrasts with results of Rose et al.,[5] where three of nine fetuses who suffered fetomaternal transfusion had some demonstrable abnormality. Fetuses who suffer fetomaternal transfusion appear to be at some risk for adverse outcome, although most will not experience problems. This group of patients is at risk for Rh sensitization in Rh-negative mothers and should be treated with adequate prophylaxis. The risk for fetomaternal transfusion is high (30.6%) after trauma during pregnancy, and if testing is not readily available to assess fetomaternal transfusion, routine administration of Rh immune globulin is recommended in addition to continuous fetal monitoring.

In conclusion, this study suggests that all patients >20 weeks' gestation who suffer trauma during pregnancy should be monitored for a minimum of 4 hours as the risk for abruptio placentae is significant and associated with frequent uterine activity. In addition, all patients >12 weeks' gestation should have Kleihauer-Betke analysis to detect fetomaternal transfusion with Rh immune globulin administration to appropriate candidates. Although only one fetus appeared to suffer any serious morbidity on the basis of fetomaternal transfusion in our series, serial testing may be indicated to substantiate that further bleeding does not occur after the initial test. If serial testing is indicated, it is not clear whether testing should occur in all patients or only those with fetomaternal transfusion present initially.

We express our appreciation to Drs. Christine Comstock, Robert Bree, and S. S. Yang for their significant contributions to this study.

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Discussion

DR. WARREN M. CROSBY, Oklahoma City, Oklahoma. This is important work. The design of the study is superb and so we can rely on the lessons learned. The authors confined their study to the group of pregnant trauma victims in which we should have the most interest: those mothers that do not have life-threatening injuries. Here the obstetrician and emergency physician can learn which maternal findings and treatments correlate best with fetal outcome. Such a study is sorely needed to provide scientific evidence on which to rely when one is advising not only the pregnant trauma victims themselves as to the likely outcome of their pregnancy but their lawyers as well, who seem bent on establishing trauma as the certain cause of a bad perinatal outcome, no matter how unlikely that conclusion seems to be.

I wish to emphasize two areas of importance:

1. I am delighted to see that 76.5% of the motor vehicle accident victims were wearing restraints. This is a much higher percentage of women drivers wearing seat belts than national surveys have found. There is little doubt that the three-point restraint, available in all automobiles today, is very effective at reducing injury. This is particularly true of the pregnant driver because belts are very successful in preventing impaction of the mother's pregnant abdomen and chest into the steering wheel. Indeed, the overrepresentation of belted victims in this study attests to this fact. Nonbelted victims that are injured at all are likely to have more serious internal injuries, injuries severe enough to prevent their having been included in this study.

2. The most important finding is that if the trauma did not produce an adverse outcome within the first day or two after the traumatic event, the trauma did not affect the pregnancy at all.

This carefully documented observation brings up the question of the so-called "delayed abruptio" following trauma. To my knowledge there have been only two cases of "delayed abruptio" reported. Both were unbelted drivers in the early third trimester.[1,2] Both hit the steering wheel and had noncatastrophic injuries. In one case the nonstress was nonreactive on admission, but clear-cut fetal compromise was not seen until the membranes ruptured 5 days later. The fetus was thought to be uncompromised in the second case for 5 days, when bleeding and contractions began. The patient was transferred to a tertiary care center and continuous fetal monitoring was not remarkable until the next day when vaginal bleeding and uterine tenderness developed along with increased uterine contractions. Late decelerations were seen and a cesarean delivery was done. Both of these fetuses were small for dates, and both lived. In both cases extensive placental separation was found.

When trauma results in disruption of the placental attachments to the decidua, the bleeding that occurs at that time is usually self-limited. When the bleeding is not self-limited, the typical signs of severe placental separation occur, beginning within the first few hours after the traumatic event. When the amount of separation is less, the blood is released into the decidua clots promptly. The decidual cells involved in the process release prostaglandins, which cause almost all trauma victims in late pregnancy to have uterine contractions. Only 7% of the victims in this study did not have uterine contractions within the first few hours after admission. Again, the process usually is self-limited. Uterine contractions stop within a few hours as they did in 91% of the victims reported here. Labor may indeed progress in some, probably related to the amount of decidual damage, the release of decidual prostaglandins, and the length of the pregnancy. In those pregnant trauma victims that are not delivered within the first 48 hours or so, the clot organization process is underway. The area of separation ultimately becomes an infarct. The process bcomes stable in virtually all cases within 24 to 48 hours of the initial event. In my opinion, the two cases of "delayed abruptio" were not "delayed" at all. It was the diagnosis that was delayed. The fetus was just so compromised that it didn't quite die initially, and diagnosis was not made until increased uterine activity or better observation a few days later called attention

to its plight. In both cases delivery occurred within 6 days of the traumatic event, and in both cases the fetus lived.

I am aware of two prospective studies of pregnant trauma victims so far unpublished, in addition to the one presented today and the one my colleagues and I reported in 1970.[3] These four prospective studies account for 797 pregnant victims of trauma. There were 17 cases of abruptio placentae among the 797 cases, and each was identified within the first few hours after the traumatic event. In short, I don't believe that there is such a thing as "delayed abruptio." The placental separation occurs at the time of the trauma and either is severe enough to cause labor, fetal death, maternal bleeding, and the like or is self-limited, with the initial symptoms of uterine contractions or spotting stopping within 48 hours in virtually every case.

Thus I agree with the authors, as well as Higgins and Garite,[2] that the fetal monitor should be applied as soon as appropriate after immediate emergency measures are taken when the pregnant trauma victim arrives at the hospital. If the fetus is far enough along to be considered viable, fetal monitoring should probably be continued for a period of a few hours to begin with. If the patient is totally asymptomatic and no evidence of injury or fetal distress can be found, it is a rare patient indeed that would return later with a dead fetus or bleeding. For patients with symptoms or signs that indicate the possibility of more severe injury, more prolonged observation in the hospital will be appropriate. I suggest that such patients have fetal monitoring during the time that they are in the hospital, because, during observation of the mother for serious injury, the fetus may very well be ignored by physicians and nurses that don't normally care for pregnant women.

But when do you stop the monitoring? When is it safe to let the patient go home? I think the best advice is to use the information presented today and tell the patient that "there are a few cases in which things turned bad several days after a traumatic event, but this is rare. It occurs much less frequently than one in a thousand cases." And then add: "But, Mrs. Smith, if you insist upon it, we'll keep you on the monitor for a full week. Since no case of trauma-related abruptio has ever been reported longer than a week later, you can go home with confidence then. This doesn't guarantee you a healthy baby. It only removes the possibility of the fetus dying from a placental separation that we haven't been able to discover." This strategy ought to allow you to let most people go home in a reasonable time. It also transfers the responsibility for going home at that time from you to the patient.

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Dr. David B. Cotton, Houston, Texas. Dr. Pearlman and his colleagues have studied 85 women suffering varying degrees of trauma during pregnancy and compared them prospectively with a control group matched for gestational age. In this study, which represents the experience of a large, sophisticated community hospital, motor vehicle accidents were the most frequent cause of trauma. Overall 97.6% of trauma cases were classified as mild to moderate and only 2.4% as critical. However, three of the five cases of abruptio placentae seen in the study, as well as two cases of preterm delivery, occurred in the minor trauma group. These five cases combine to give a 6.7% incidence of immediate adverse outcome in minor trauma cases, which are defined as minor bruising, lacerations, or contusions. This information emphasizes strongly that even minor trauma during pregnancy must be taken seriously by the obstetrician and a consistent and thorough evaluation implemented.

The incidence of fetomaternal transfusion in the trauma group was 30.6% as compared with 8.2% in the control group. The mean volume of fetomaternal transfusion in the trauma group (12.2 ml) was three times that of the control group (3.2 ml). Additionally, an anterior placental location site appeared to be much more susceptible to trauma as fetomaternal transfusion was twice as frequent in anterior placentas than other placental locations.

Importantly, for those evaluating pregnant trauma victims, uterine tenderness was associated with a fetomaternal transfusion 65% of the time. However, 32% or roughly one third of patients with a demonstrable fetomaternal transfusion had no significant uterine tenderness.

Additionally, in this group undergoing fetal monitoring for a minimum of 4 hours there was no relationship between uterine activity or fetal heart rate tracing abnormalities and the risk of fetomaternal transfusion. It would appear from these data that there are no clinically reliable signs or symptoms that predict fetomaternal transfusion in trauma cases. In cases of even minor trauma involving Rh-negative patients a Kleihauer-Betke test must be considered mandatory.

Ninety-three percent of patients in this study had some uterine activity following trauma. In this protocol all patients with uterine contractions more frequent than one every 10 minutes were admitted for a 24-hour observation period. All patients experiencing immediate adverse outcomes had contractions every 2 to 5 minutes (group IV) at some time during the initial 4-hour monitoring period. The data from this study suggest that a simple 4-hour fetal monitoring period combined with a Kleihauer-Betke screen will identify virtually all the fetal morbidity associated with trauma in pregnancy.

Last, and for the patient perhaps most important, this study documents that when pregnant patients undergo trauma but do not have an immediate adverse

outcome there are no subsequent effects on maternal, fetal, or neonatal outcome.

Questions that this study raise include the following:

1. Is William Beaumont Hospital a level I referral center for trauma? If not, perhaps this explains the relatively low incidence of critical trauma.

2. Was there a gestational age below which immediate adverse outcomes such as abruptio placentae or preterm delivery did not occur in the minor trauma group? Perhaps minor trauma before 20 weeks' gestation rarely results in immediate adverse outcome.

3. In those patients with minor trauma and abruptio placentae or preterm labor did each patient experience a blow specifically to the abdomen?

4. Is the 8.2% incidence of fetomaternal transfusion in the control group somewhat higher than one would normally expect?

5. What was the incidence of fetomaternal transfusion in the minor versus moderate trauma group and were these mostly concentrated in the late third trimester?

6. Last, although this study has defined the incidence and degree of fetomaternal transfusion with trauma during pregnancy, what is the purpose of documenting fetomaternal transfusion in patients who are Rh-positive if management primarily hinges on fetal heart rate monitoring?

The authors are to be congratulated for a well-designed, clinically relevant study.

Dr. Charles A. Stedman, New Orleans, Louisiana. There have been several studies of ≥1000 consecutive Rh-negative patients who after the ultimate trauma, the delivery process, have been found to have significant fetal-maternal hemorrhage. Only three to ten patients per thousand have been noted under those circumstances. How do the authors explain the fetal-maternal hemorrhage incidence of 80 per thousand in their control group? This suggests some sort of method error in the laboratory.

The second question is do they get their Kleihauer-Betke results back within 4 hours? At most institutions a pathologist is required to give those results. In most of the hospitals in which I've worked, the pathologist is unavailable at nighttime, and we have to wait until the next morning for results.

Dr. Sharon L. Dooley, Chicago, Illinois. I think this is a wonderful study that tremendously advances our knowledge. I have a comment about terminology. Dr. Pearlman used the term *severe fetal acidosis* to show the cord artery pH values for the fetuses that required urgent delivery. For a long time, and for reasons that are not clear, we used a pH of 7.20 as the lower limit of normal for cord artery pH. There are now considerable data published that indicate that the lower limit of normal is closer to 7.10 or 7.12 and that a pH really has to be less than 7.00 before we call that a severe fetal acidemia.

I think it's time for us all to stop "digging our own graves" for the lawyers and use proper terminology.

Dr. James R. Scott, Salt Lake City, Utah. I wonder if you could give us details about the management of the cases of abruptio placentae and specifically what happened with the one stillborn infant. The reason I ask is that many of these fetuses are premature when being monitored, and we consider it to be ominous if there are any abnormalities. I can recall at least one patient who was being monitored and the fetal heart rate suddenly dropped to zero.

Dr. Daniel A. Rightmire, Springfield, Illinois. Do the authors have information about biochemical assays, such as maternal serum α-fetoprotein or β-human chorionic gonadotropin, which might be markers of trophoblast injury or death available in a hospital that does not have reliable Kleihauer-Betke techniques?

Dr. Pearlman (Closing). Dr. Cotton, Beaumont Hospital's emergency center is a level I trauma referral center and sees approximately 75,000 patients per year. However, because of its suburban location, we do not see the same frequency of severe trauma as an inner city institution.

The earliest gestational age at which we saw an immediate adverse outcome was 26 weeks—an abruptio placentae. However, I would not discount the possibility of abruptio placentae before that gestational age as it most definitely occurs. Prior studies have also shown that the more advanced a pregnancy is, the more susceptible the fetus and placenta are to injury.[1]

The issue of whether patients experienced a direct blow to the abdomen is particularly problematic. When patients who have been involved in motor vehicle accidents are asked if they've been struck directly in the abdomen, the answer is not always reliable. Many patients that we saw who stated they were not struck in the abdomen had seat belt bruises or other evidence of injury to the abdomen, so I don't think you can rely on history alone. In terms of immediate adverse outcome, all our patients, either historically or by examination, had evidence of a direct blow to the abdomen.

The incidence of fetomaternal transfusion in our control group was approximately 8%, which is similar to the 6% reported by Rose et al.[2] in their prospective trauma study's control group. In addition, there are two additional studies that evaluated the incidence of fetomaternal transfusion in normal pregnancies, revealing some evidence of fetomaternal transfusion in at least 5% to 10% during the third trimester, although they did count 5×10^4 maternal cells.[3, 4] I think that our results are similar to these studies.

With regard to the relationship between fetomaternal transfusion and gestational age, most of these injuries occurred during the third trimester, so a majority of transfusions were found in this group. However, we saw evidence of fetomaternal bleeding in a pregnancy of 15 weeks. So I think that the 12-week limit for testing is reasonable (i.e., when the uterus becomes an abdominal organ and is susceptible to injury).

As Dr. Cotton stated, the major purpose of documenting fetomaternal transfusion is to decrease the incidence of Rh isoimmunization in the Rh-negative patient. However, one of the fetuses in this study suffered a 69 ml transfusion and on continued monitoring had an aminous fetal heart tracing. The fetus was delivered

and was severely anemic at birth, requiring blood transfusion. That was our only complication related directly to fetomaternal transfusion. The only other study that prospectively evaluated fetomaternal transfusion after trauma exhibited even a higher frequency of complications related to the fetomaternal transfusion.[2] So I think that Kleihauer-Betke testing in all patients, whether Rh negative or Rh positive, is justified.

Regarding the question about the use of the term *fetal acidosis,* I agree that the nomenclature is evolving with regard to defining fetal acisosis; however, I think it is clear that three of the four venous pH values are lower than what we generally consider to be normal.

Dr. Scott asked about the history of the stillborn infant. That case report actually is already published.[5] Briefly, this was a woman at 32 weeks' gestation whose car was struck by a cement truck, and she was trapped inside the car for approximately 45 minutes. Her fetus was dead on presentation to the emergency center. The patient also had multiple severe intraabdominal injuries and underwent laparotomy. Cesarean section was done at the time of laparotomy because she also had an unstable pelvic fracture. The placenta was anterior and completely separated from the uterine wall, which explains the fetal loss. There was no evidence of direct fetal injury on examination of x-ray film.

We do not have any information on β-human chorionic gonadotropin or maternal serum α-fetoprotein in these patients. I would like to mention two things regarding maternal serum α-fetoprotein for assessing the need for isoimmunization prophylaxis. First, you cannot accurately determine the volume of the transfusion that prohibits the reliable administration of Rh immune globulin. Second, you would need a preinjury maternal serum α-fetoprotein level to determine the presence of fetomaternal bleeding, and this may or may not be available.

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Biochemical evaluation of endometrial biopsies by magnetic resonance spectroscopy—Preliminary data

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Biochemical study of tissue biopsy samples by magnetic resonance spectroscopy involves relatively small capital and running costs and could become a routine diagnostic or screening procedure if its utility were to be adequately demonstrated. We have demonstrated feasibility of evaluation of endometrial biopsy samples by magnetic resonance previous to histopathologic examination. Preliminary comparisons of magnetic resonance spectra with histopathologic evaluation indicates that in at least some instances, magnetic resonance may be the more sensitive indicator of disease. (AM J OBSTET GYNECOL 1990;162:1511-7.)

Key words: Magnetic resonance spectroscopy, magnetic resonance imaging, 31-P nuclear magnetic resonance, endometrial carcinoma, histology, biospy samples

The first clinical investigation with magnetic resonance was undertaken by an obstetrician and gynecologist. In their pioneering work, Odeblad and Bryhn[1] used magnetic resonance to study properties of mucous secretions from the cervical glands and predicted that magnetic resonance would be useful in clinical diagnosis. Their predictions have been realized by the presence of magnetic resonance imaging (MRI) facilities associated with hospitals and medical centers throughout the world. Whereas MRI has become a familiar tool to physicians, magnetic resonance spectroscopy (MRS), which allows the noninvasive investigation of the metabolism of cells and tissues, is less well known. The potential of MRS in detecting and monitoring biochemical alterations in diseased tissues was first shown in studies of Duchenne muscular dystrophy and a variety of metabolic myopathies.[2,3] These and subsequent studies have raised the hope that diseases might be detected by noninvasive monitoring of cellular biochemistry.

The past decade has seen enormous advances in MRI and MRS techniques, and it is now possible in some centers to obtain spatially resolved metabolic information in normal individuals and patients. However, although virtually all of the effort to develop clinical applications of MRS is focused on localized spectroscopy in conjunction with MRI, such examinations are expensive and thus limited to cases of clear need. We are exploring the alternative possibility that MRS of biopsy samples, with its relatively low capital and running costs, could become an effective supplement to histologic evaluation, or be used as a mass screening method for early detection of some gynecologic diseases.

Our interest in this possibility grew as a result of findings in our own and other laboratories[4-7] that MRS of female reproductive tissues shows specific characteristics that change with physiologic status and with common pregnancy disorders and gynecologic diseases. We have therefore designed and built a double tuned phosphorus 31 and proton probe for rapid and nondestructive MRS of endometrial biopsy samples that are subsequently evaluated histologically. Preliminary comparisons of nuclear magnetic resonance spectra of myometrium and endometrium with histopathologic evaluation indicates that in at least some instances, MRS may be the more sensitive indicator of the presence of disease.

Material and methods

Endometrium was aspirated from two normal volunteers during the proliferative and secretory phases of the menstrual cycle. Endometrial samples were obtained from eight patients by aspiration or by curettage of the hysterectomy specimens, and a total of 11 diseased myometria have been examined. Sections of hysterectomy samples (both endometrium and myometrium) were taken such that diseased tissued, grossly normal tissue at the site of disease, as well as tissue far removed from the diseased area were obtained. In-

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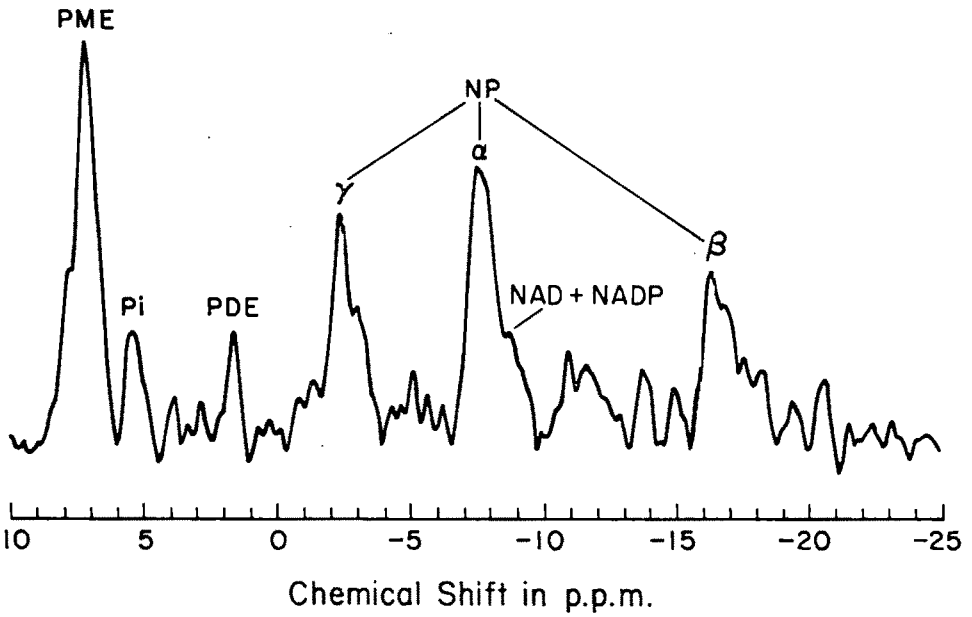


Fig. 1. ^{31}P magnetic resonance spectrum of proliferative endometrium obtained by aspiration from a normal volunteer. The tissue was bathed in oxygenated De Jalon's solution at 4° C within a home-built small-sample MRS probe and the spectrum obtained over a 4-hour period as described in Methods. *PME,* Phosphomonoester; *Pi,* inorganic phosphate; *PDE,* phosphodiester; *PCr,* phosphocreatine; *NP,* nucleoside phosphates; *NAD + NADP,* pyridine nucleotides; *UDPG,* uridine disphosphoglucose.

formed written consent was obtained in all cases and the study was approved by the Institutional Review Board of the University of Illinois.

All samples were immediately placed in physiologic salt solution (De Jalon's solution) that was precooled and prebubbled with a mixture of 95% oxygen and 5% carbon dioxide gases. The samples were immediately transported on ice in a thermally insulated box to the spectrometer.

^{31}P nuclear magnetic resonance spectra were obtained with a vertical high-resolution wide-bore spectrometer (GN300, General Electric, Freemont, Calif.) operating at 121.5 MHz. Spectra from hysterectomy samples (2 to 5 gm) were acquired with a 20 mm conventional probe with 20 μsec pulse duration at 1.5 second intervals, averaged over 50 minutes. Biopsy samples (50 to 100 mg) were studied (15 μsec pulse duration at 500 ms intervals, averaged for approximately 4 hours) in a home-built small-sample probe[8] that contains a flattened solenoidal radio frequency coil immersed in Fluorinert (purchased from 3M, Minneapolis, Minn.) and mounted horizontally. The acquired signals were exponentially multiplied by 30 Hz, but no other signal enhancement procedures were applied. Resonance frequencies of the phosphorus signals were measured in relation to that of an internal standard (phosphocreatine, or in its absence, the α-nucleotide phosphate peak) in parts per million. Positions of the internal standard were verified by use of an external standard of 0.1 mol/L hexachlorocyclotriphosphazene (purchased from Aldrich, Milwaukee, Wis.). Data analysis was performed as described previously[7] except that absolute calibration of peak intensities was not attempted. Tissues were placed in formalin and returned to the pathologist after the MRS study was concluded. The time from obtaining the specimen to placing it in formalin was approximately 5 hours for the biopsy specimen and 1 hour for the hysterectomy samples.

Results

Fig. 1 shows a ^{31}P spectrum of proliferative endometrium obtained by aspiration from a normal volunteer, and maintained in oxygenated physiologic salt solution. The peaks show the presence of nucleoside phosphates, primarily adenosine triphosphate, uridine diphosphoglucose, inorganic phosphate, and multiple peaks in the phosphomonoester and diester regions of the spectrum. These assignments are based on previous ^{31}P studies of similar tissues. The phosphomonoester region contains contributions from phosphoryl derivatives of choline and ethanolamine, which are precursors of membrane phospholipids, and perhaps also from sugar phosphate intermediates of metabolism. The phosphodiester region of the spectrum of living tissues typically contains resonances from glycerol-phosphoryl choline and glycerol-phosphoryl ethanol-

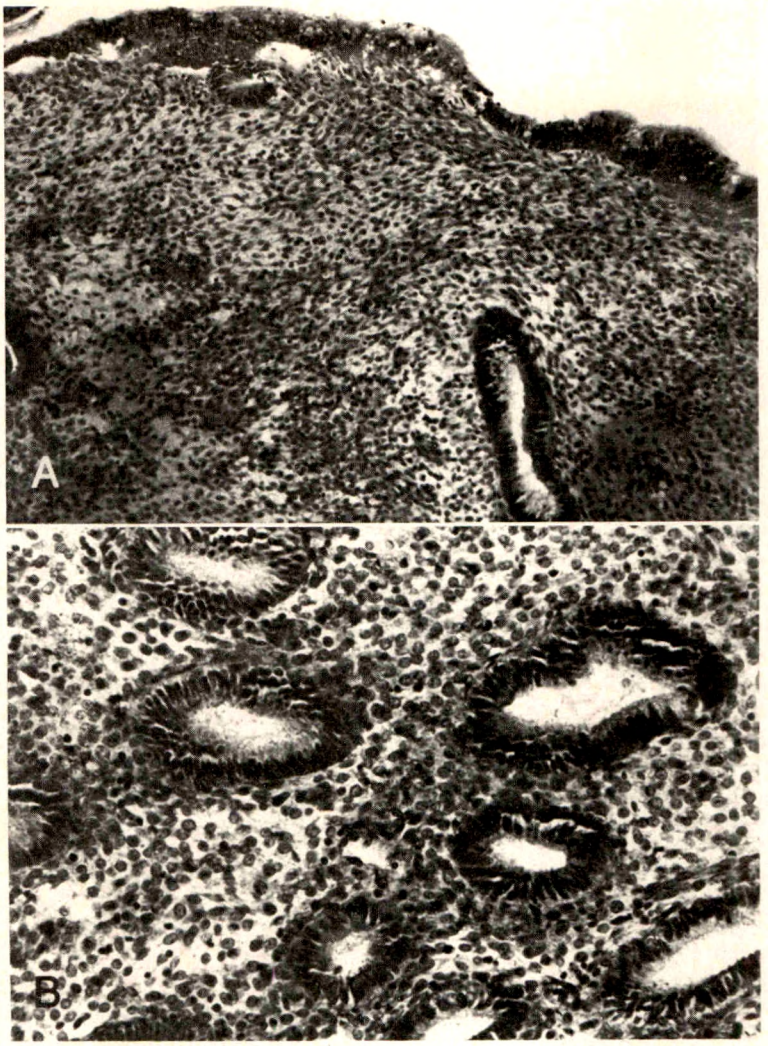


Fig. 2. Hemotoxin and eosin-y stain of the normal proliferative endometrium from which the spectrum shown in Fig. 1 was obtained. The specimen was preserved in formalin after MRS examination in a 7 Tesla magnetic field. **A,** Endometrial epithelium. (Original magnification ×160.) **B,** Integrity of the endometrial glands. (Original magnification ×640.)

amine, which are membrane phospholipid degradation products. Resolution of the phosphomonoester and diester regions of the spectrum of endometrial samples into their individual components requires MRS studies of extracts prepared from this tissue, or, alternatively, studies of the living tissue in the presence of a higher magnetic field.

Fig. 2 shows the histologic sections prepared by the pathologist from the tissue that yielded the spectrum shown in Fig. 1. The pathologist reported no deterioration and thus no difficulty in evaluating the presented tissue; as shown in Fig. 2, both glands and epithelial membranes are well preserved. Samples that have been investigated by MRS and subsequently evaluated by histology include proliferative (n = 3) and secretory (n = 1) endometrium obtained from normal volunteers as well as endometrial and myometrial samples obtained from patients who had hysterectomies because of multiple leiomyomas (n = 8), adenomyosis (n = 2), and endometrial hyperplasia (n = 1). In all 15 cases the tissue samples appeared to be unaffected by the MRS evaluation.

Comparison of spectral and histologic characteristics of biopsy and hysterectomy samples is now underway. We have obtained specimens of grossly abnormal tissue (representing the diseases previously listed), tissue that appears to be normal by gross inspection but is as near as feasible to the site of the lesion, and tissue located a few centimeters distant from the lesion. We also obtained samples of endometrium in cases of myometrial lesions and vice versa. Our preliminary studies on the 11 cases investigated by both MRS and histologic analysis indicate that histologically normal tissue obtained a few centimeters distant from a lesion of the same

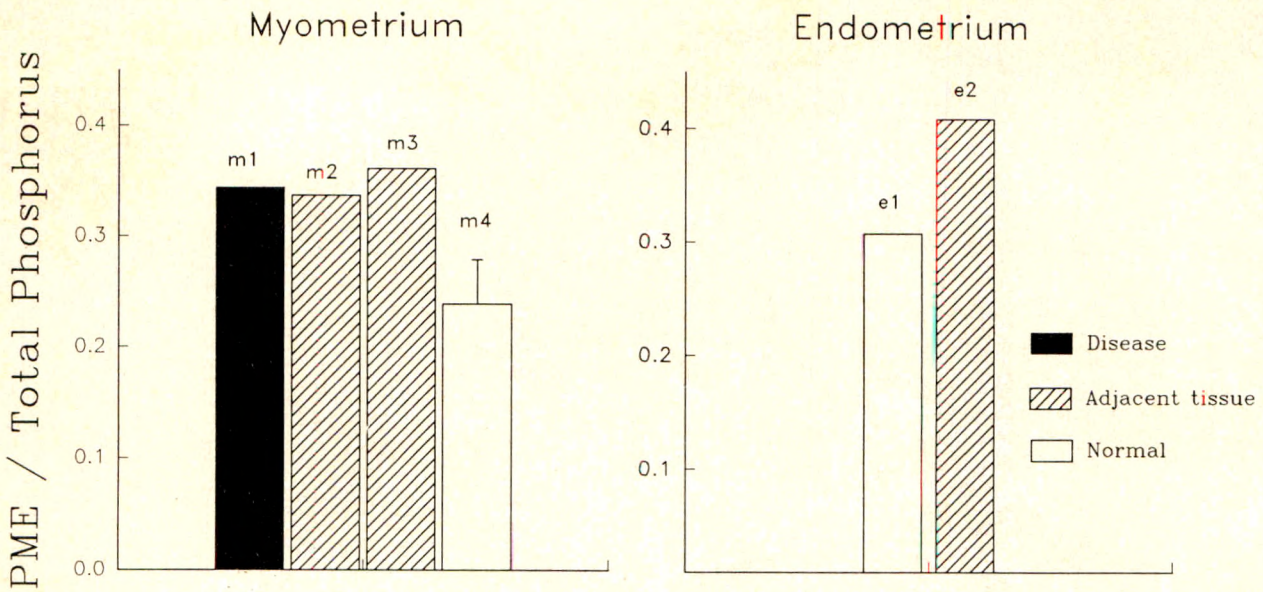


Fig. 3. The effect of leiomyoma on phosphomonoester levels of adjacent tissue in the human myometrium and endometrium. Histogram of the signal intensity in the phosphomonoester region divided by the total measurable intensity in the ^{31}P spectrum. Myometrial and endometrial tissues were obtained from the uterus of a 38-year-old patient who had a hysterectomy for multiple leiomyomas. Myometrium: *m1*, a single specimen of a subserosal leiomyoma; *m2*, myometrial tissue sectioned immediately adjacent to the site of the leiomyoma. Histologic study revealed the presence of both normal and abnormal tissue; *m3*, myometrial tissue section more than 5 cm away from the site of the lesion. Histologic study revealed only normal myometrium. *m4*, Mean and standard error of results on 12 normal myometrial specimens from our earlier study.[7] Endometrium: *e1*, average of two control values obtained from tissue aspirated from healthy volunteers at the same stage of the cycle; *e2*, endometrial curettage close to the diseased area of the myometrium.

tissue type shows abnormally high intensity in the phosphomonoester region of the spectrum. For example, histologically normal tissue obtained within 5 cm of a leiomyoma has a 1.2-fold increase in phosphomonoester, compared with controls (8 cases, 12 controls, $p < 0.03$). In addition, the leiomyomas appear to be associated with abnormalities in spectra from adjacent endometrium and endometrial lesions are associated with abnormalities in spectra of adjacent myometrium. These spectral abnormalities are particularly apparent in the phosphomonoester region.

Our preliminary findings are exemplified by the data shown in Fig. 3, obtained from a patient with multiple leiomyomas. As shown by the bar graph, the leiomyoma shows high phosphomonoester peak intensity compared with control values obtained in a previous study.[7] The high phosphomonoester of the leiomyoma is also observed in histologically normal tissue as far as approximately 5 cm distant from the lesion. In addition, there is a relative increase in the intensity of the phosphomonoester peak in the spectrum from the endometrial tissue curettage from near the site of the leiomyoma compared with endometrial tissue obtained by aspiration from two normal volunteers.

Comment

In this preliminary study we have obtained meaningful ^{31}P magnetic resonance spectra from endometrial biopsy samples, and can therefore conclude that biochemical evaluation of endometrial biopsy samples by MRS is feasible. We have also found that there is no deterioration of the specimen as a result of the MRS analysis of the biopsy. Thus the first prerequisites for use of MRS in conjunction with histology of biopsy samples is satisfied, leading to possible applications in gynecology and other clinical fields.

MRS studies of tissue biopsy samples involve relatively small capital and running costs and could therefore become routine diagnostic or screening procedures if their use were to be adequately demonstrated. Our preliminary studies are promising in that comparison of MRS with histopathologic evaluation indicates that in at least some instances MRS may be the more sensitive indicator of the presence of disease. This is exemplified by apparent changes in the phosphomonoester region of the spectrum in histologically normal tissue near the sites of endometrial or myometrial lesions. Metabolites that give rise to signals in the phosphomonoester region of the ^{31}P spectrum are cyto-

plasmic constituents, and have never been found in extracellular fluids or bathing medium; thus diffusion from the site of formation appears to be an unlikely explanation for our results. Our results are consistent with a number of reports that phosphomonoester intensity is elevated in diseased tissue, including benign and malignant neoplasm. Particularly relevant is the finding that phosphomonoester peak intensities are elevated in breast cancers, and are higher in malignant than benign breast tumors.[9]

Further study will be required to fully characterize the biochemical changes that occur in histologically normal tissue that is in proximity to uterine lesions. In addition, these preliminary results suggest that further development of small-sample spectroscopic techniques is worthwhile. We are currently improving our probe design and evaluating novel methods of extracting NMR signals from noisy spectra. Finally, application of additional magnetic resonance techniques, including analysis of other magnetically sensitive nuclei, may prove equally fruitful to the ^{31}P studies described here.

We thank Dr. Y. T. Ho and Ms. Della Moon, Department of Pathology, Burnham Hospital, Champaign, Illinois; and Dr. S. Nandkumar, Assistant Professor of Pathology, College of Medicine, University of Illinois, Urbana-Champaign, for their help and advice. We acknowledge the cooperation and help of the graduate students in the laboratory, especially Brian B. Roman, and members of the staff at Womens' Health Practice, Champaign, Illinois.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. J. G. Quirk, Little Rock, Arkansas. Significantly, the first clinical investigation that used MRS studied proton magnetic resonance of human cervical mucus during the menstrual cycle. That pioneering study by Drs. Odeblad and Bryhn was published in 1957.[1] Over the past 6 years investigators led by Dr. Joan Dawson at Urbana-Champaign have accelerated the application of MRS to studies of both the normal and diseased female reproductive tract.

The development of MRS in biology is based on the fact that certain atomic nuclei found in relative abundance in biologic material—^{1}H, ^{13}C, ^{31}P—will absorb radiation at characteristic frequencies when they are oriented by a strong magnetic field. Importantly, nuclei of the same element, when found in different chemical environments, absorb energy at different frequencies. This displacement of the resonance frequency from some chosen reference frequency produces distinct, so-called chemically shifted spectral lines. As a result it is possible to observe specific atoms, for example, phosphorus in the α-phosphate group of adenosine triphosphate, even in complex solutions or in the solid state.

This article represents preliminary data in the authors' continuing attempt to correlate disease state in the female reproductive tract with alterations in ^{31}P MRS. Data are presented that suggest that phosphomonoester is elevated in all tissues (myometrium, myoma, endometrium) obtained from a uterus removed for uterine leiomyomas. This preliminary result parallels their previous findings in myometrial tissue obtained from uteri containing adenocarcinoma[2] and is supported by other studies of cultured colonic adenocarcinoma cells and metastatic adenocarcinoma of the liver.[3,4] In addition, the authors have demonstrated previously that, compared with the normal nongravid uterus, tissue obtained from the gravid uterus at term contains an excess of phosphodiesters, phosphocreatine, and uridine diphosphoglucose.

In aggregate, the authors have thus far described the ^{31}P magnetic resonance spectra of myometrium and endometrium in the pregnant and the nonpregnant state, in the presence and absence of endometrial adenocarcinoma, and in the presence and absence of uterine leiomyomas. They have demonstrated consistent but variable changes in spectra effected by the endocrine milieu and pathologic status of these tissues. Of particular interest to me are the changes in precursors

and products of membrane glycerophospholipids described in their work. I must admit that I cannot at this time interpret these results, but it would be reasonable to assume that these findings reflect alterations in the activity of the enzymes that regulate membrane metabolism and signal transduction across the plasma membrane.

Pregnant women and women with adenocarcinoma of the endometrium are known to express several of the protooncogenes.[5,6] The products of some of these genes varicusly alter signal transduction across the plasma membrane, have protein kinase activity, or regulate adenylate cylase, all processes intimately involved with phosphate metabolism. It would be exciting to learn if changes in ^{31}P MRS associated with these conditions could be correlated in a meaningful way with the expression of protooncogenes known to affect the metabolism of phosphorus-containing compounds within these cells.

I have several questions for the authors about the article. (1) In the Material and methods section, you state that absolute calibration of peak intensities was not attempted. If this is true, can we be certain that the fraction of the total phosphorus signal that is contained in the phosphomonoesters is truly elevated? (2) Because you suggest that MRS analysis of biopsy samples is less expensive than in vivo magnetic resonance spectroscopy, could you give us an idea of the present capital investment and running costs for this equipment? (3) Have you been able to extend your findings to myometrial specimens obtained for other pathologic states? (4) What are the prospects for resolving individual clinical moieties contained in the phosphomonoester and phosphodiester peaks?

Only 20 years ago, clinically useful imaging science was limited to reading x-ray films and looking down the barrel of a microscope. Today the clinical utility of real-time ultrasound including Doppler, computerized tomographic scans, magnetic resonance imaging, and electron microscopy are all accepted as routine. Recent developments in MRS such as these described today will succeed ultimately in making it the youngest child in the family of imaging sciences.

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Dr. Louis H. Weiland, Scottsdale, Arizona. Recognition of disease states in tissues have relied on microscopic examination for the past century and the usefulness of such methods is well recognized. However, with earlier detection of disease recognition of morphologic microscopic changes becomes diminishingly subtle. In recognition of this fact, the authors report on their attempt to recognize disease states of uterine tissues biochemically, by means of relatively new technology. Specifically, they have submitted uterine tissues to MRS with measurements of ^{31}P. Phosphorus exists within the cell as inorganic phosphorus and as many organic compounds composing metabolites and components of cell structure. Since this is a noninvasive (at a cellular level) technique, the specimens can be further submitted for histologic study. The early and very limited results suggest the possibility of quantitative differences in their measurements of diseased versus normal tissue.

A critical problem in MRS when performed in vitro is maintaining cells in their natural physiologic state. Endometrial tissue has a relatively high metabolic rate and it is questionable whether the authors were successful in maintaining this natural state with their stated techniques. The fact that the tissues appeared well preserved on histologic examination is not adequate proof that their physiologic processes were not significantly altered. Hopefully, this study will be an introduction to what might be an exciting and useful method of noninvasively examining cells and determining the presence (or absence) of a disease state.

Dr. Daniel A. Rightmire, Springfield, Illinois. Has the research team had the opportunity to examine specimens with electron microscopy in addition to light microscopy after MRS with their new probe?

Ms. Raman (Closing). It was indeed a great opportunity for me at this stage of my graduate career to realize the impact of this type of basic research and obtain feedback from clinicians who will use or exploit the potential of this new technique.

I must mention (and probably reiterate something that Dr. Quirk and Dr. Weiland mentioned) that MRS or even MRI of reproductive tissues had been neglected until the last few years. Although the very first clinical study was by Odeblad, who himself was a Swedish obstetrician and gynecologist, no one studied these tissues until the 1980s when Professor Dawson studied the effects of pregnancy on the rat uterus. Therefore it is indeed encouraging to see that additional research is developing in this area. It is probably quite likely that there will be a tremendous growth of applications of MRS to the specific field of obstetrics and gynecology.

Dr. Quirk raised the question of absolute calibration. In this stage of our study, we did not want to obtain

absolute quantities of substances (i.e., we did not want to say there were so many millimoles of phosphomonoesters in this tissue versus that), primarily because absolute calibration takes longer than the rapid pulsing that we now utilize. Since we are comparing the same ratios for the normals and controls, those are not variable, and therefore there is indeed a relative elevation of phosphomonoester intensity reported in this article.

The cost of obtaining biopsies by NMR was also questioned. If we assume that we have bought an NMR spectrometer, which is the main expense, on an hourly basis some outside collaborators are charged approximately $10 to $12 for an hour of experiments on this machine. We calculated that for the time needed for a biopsy experiment of about 6 hours, including all the costs of doing the biopsy, it is approximately $50, or slightly less, for one particular experiment.

That point was raised merely to suggest that even though MRI is currently a popular diagnostic tool, MRS should not be neglected because there is a definite savings, not only in cost, but we can also obtain a new perspective on the tissues under study.

What about the phosphomonoester peak? Can the individual phospholipids there be resolved? This was an interesting question because that is a question that I am pursuing currently. As you progress to a higher field strength magnet, the spectrum itself can expand so that other constituents of each peak are resolved and they can be observed individually. For instance, phosphomonoesters are basically phosphoryl choline and ethanolamine. You can see the individual peaks when you go to a higher field magnet, and you can get quantities of the particular compound that is causing that change in phosphomonoester. Extracts of the tissue should also be performed for identifying individual phosphomonoesters.

Dr. Weiland commented on MRI and MRS and compared them, and that was an interesting comparison. I must state that there have been reports earlier and as recently as a few months ago in a radiology article in which investigators studied bone and soft tissue lesions and performed biopsies on them; they could not obtain all the information from their proton imaging. They performed phosphorus nuclear magnetic resonance studies and were able to obtain a greater amount of information and thereby a better prognosis.

Dr. Weiland asked the question of why we are studying endometrium and myometrial tissues. We have done studies on nonpregnant and pregnant uteri. We have studied the placenta in the three trimesters, and have also looked at fallopian tubes and ovaries. As I mentioned, this is just one aspect of my project involving myometrial and endometrial tissues; I am trying to realize the application of MRS to the entire field of reproductive tissues.

With regard to preserving the tissue in a physiologic solution, phosphorus spectroscopy itself is used to study whether a tissue has been preserved or not. There are several groups that are studying the viability of placentas after they are removed and are trying to do experiments on them. One group of researchers is trying to determine whether the placenta can be maintained in a living condition once it is removed. There is proof that there is a comparison between the results of our isolated studies and the in vivo studies.

Only recently, at a conference in Amsterdam, a group from the United Kingdom reported the first in vivo studies of human placenta. Their spectra compare well with our spectra. Therefore, once we know the actual amount of adenosine triphosphate that should be present in the placenta or in these tissues and if we can maintain those same high levels during experimentation, we can be fairly sure that the tissue is biochemically well preserved.

Dr. Weiland discussed other kinds of nuclei that can be exploited. Currently, phosphorus is very popular for studies of living systems because it provides a direct insight into the metabolic processes since adenosine triphosphate is a phosphorus compound and the other membrane constituents are phosphorus compounds.

In conclusion, I am encouraged by the feedback I have received from this forum; it is indicative of the fact that my initial work will probably be fruitful if such encouragment is sustained.

The diagnostic efficacy of the umbilical arterial systolic/diastolic ratio as a screening tool: A prospective blinded study

Dev Maulik, MD, PhD, Prasad Yarlagadda, PhD, James P. Youngblood, MD, and Pamela Ciston, RDMS

Kansas City, Missouri

This prospective blinded study investigated the diagnostic efficacy of the umbilical arterial systolic/diastolic ratio performed at 34 to 36 weeks' gestation for identifying pregnancies at a high risk for adverse perinatal outcomes. A series of 350 consecutive singleton pregnancies were included in the study. A continuous-wave Doppler instrument with a 4 MHz transducer was used. The criteria for an abnormal perinatal outcome included intrauterine growth retardation, an Apgar score of <7 at 5 minutes, umbilical arterial pH at birth <7.20, presence of thick meconium, fetal distress in labor, and neonatal complications necessitating admission to the neonatal intensive care nursery. The analytic techniques included determination of the receiver operating characteristic curve, sensitivity, specificity, positive and negative predictive values, and the kappa index. The results demonstrated that although the cutoff value of 2.9 showed the maximum inherent discriminatory power, its diagnostic efficacy (sensitivity, 0.83; specificity, 0.87 positive predictive value, 0.74; negative predictive value, 0.92; and kappa index, 0.68) was not substantially different from that of the more common cutoff value of 3.0 (sensitivity, 0.79; specificity, 0.93; positive predictive value, 0.83; negative predictive value, 0.91; and kappa index, 0.73). Both values were rated good to excellent by the kappa index. The study also demonstrated that the systolic/diastolic ratio was a better predictor of general abnormal outcome than of the suboptimal fetal growth. (AM J OBSTET GYNECOL 1990;162:1518-25.)

Key words: Doppler, systolic/diastolic ratio, abnormal outcome, diagnostic efficacy

Recent experience suggests that the Doppler velocimetry of the umbilical arterial flow can be of potential benefit as a fetal surveillance tool. However, any such use of the Doppler technique requires (1) an understanding of the various factors that contribute toward its variance, (2) an unbiased demonstration of its diagnostic efficacy, and (3) a randomized clinical trial to demonstrate that the use of the technique leads to an improved perinatal outcome. Previously, we defined some of the factors that influence the variability of the Doppler indices measured in the umbilical artery.[1] In this component of our ongoing project, we present our results from a prospective blinded study that investigated the diagnostic efficacy of umbilical arterial Doppler ultrasonography in the last trimester of pregnancy as a screening test for identifying high-risk fetuses. Specifically, the investigation aimed to assess the inherent discriminatory ability and diagnostic accuracy of various cutoff values of the umbilical arterial systolic/diastolic ratio measured at 34 to 36 weeks' gestation in identifying those pregnancies that are at high risk for an adverse perinatal outcome.

From the University of Missouri at Kansas City School of Medicine.
Central Association Award, presented at the Fifty-seventh Annual Meeting of the Central Association of Obstetricians and Gynecologists, Scottsdale, Arizona, October 12-14, 1989.
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6/6/20161

Methods and material

The patient population consisted of a series of 350 consecutive singleton pregnancies at 34 to 36 weeks' gestation. Most patients were medically indigent. The investigation was conducted with the approval of the Institutional Review Board and informed consent was obtained. Each patient had a single Doppler examination that was performed with a continuous-wave instrument with a 4 MHz transducer (Multigon, Inc., Vernon, N.Y.). The method of examination has been described previously.[2] The results of the examination were not made available for clinical management. The perinatal outcome was considered abnormal when any one or combination of the following parameters was present: small-for-gestational age (SGA, <10th percentile), an Apgar score <7 at 5 minutes, umbilical arterial pH at birth <7.20, presence of thick meconium, fetal distress in labor (late decelerations, severe variable decelerations, absence of variability, fetal scalp pH <7.20),

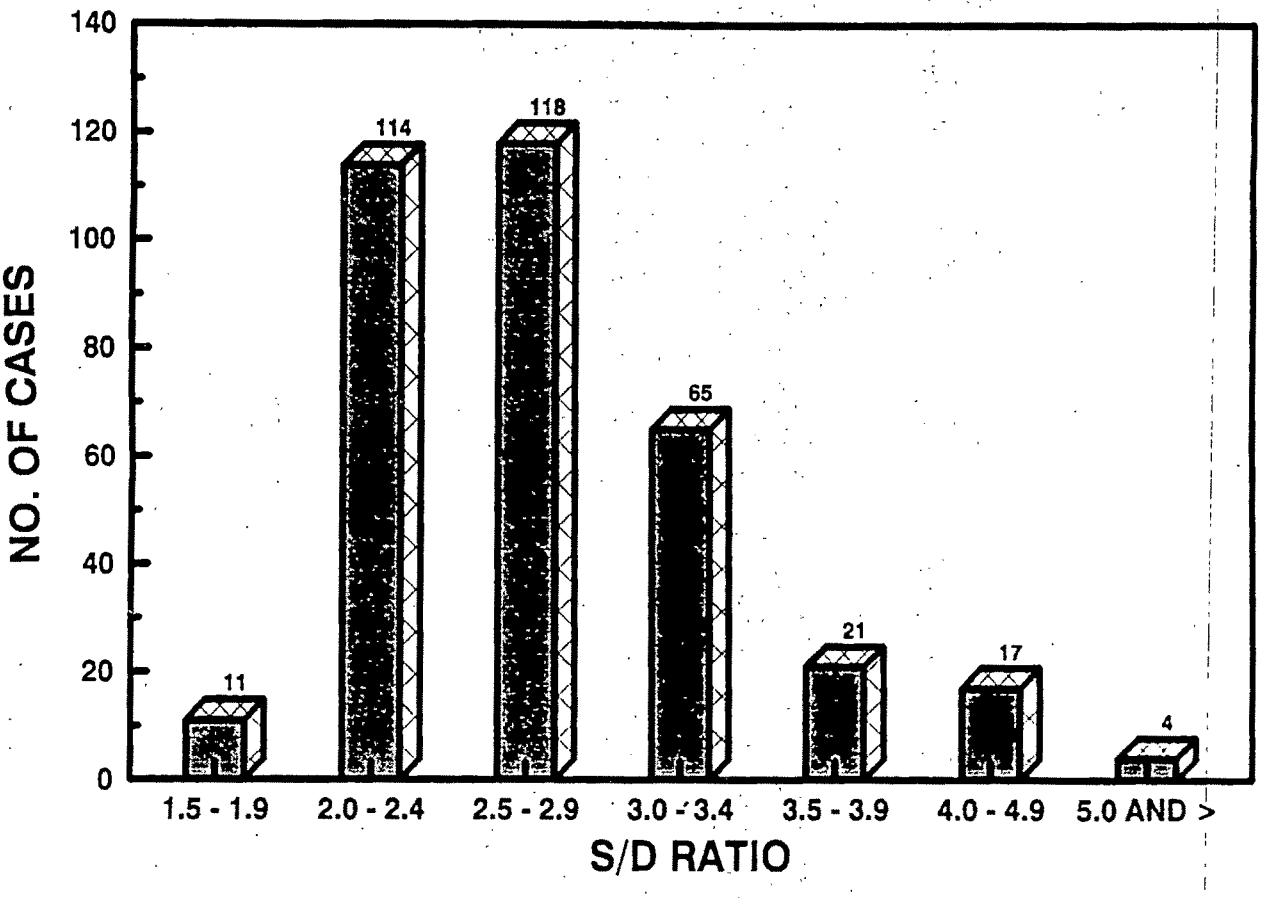


Fig. 1. The distribution of the umbilical arterial systolic/diastolic ratio in the study population. Note its non-Gaussian distribution.

and neonatal complications necessitating admission to the neonatal intensive care nursery.

To determine the optimal value of systolic/diastolic ratio for identifying the fetus at risk, the probability density distribution of the systolic/diastolic ratio among the normal and abnormal outcome groups and the receiver operating characteristic analytic technique, described by Weinstein et al.,[3,4] were used. The receiver operating characteristic technique offers a powerful tool for determining the inherent discriminative power of a clinical test.[3,4] The receiver operating characteristic curve graphically depicts the changes in the true-positive rate and the false-positive rate with respect to one another in relation to a series of cutoff points of the test value. The point closest to the upper left corner of the graph (depicting the cutoff value with the maximum true-positive and minimum false-positive rates) represents the greatest intrinsic ability of the test to discriminate between normal and abnormal population groups. This curve thus assists in selecting the test value best suited to separate those who are at high risk from those who are at low risk. The performance of the test at the selected value was expressed in terms of sensitivity, specificity, and the positive and negative predictive values. Finally, the extent of agreement between the test results and the outcomes, that could not be attributable to chance, were assessed using Cohen's kappa index[5] according to the method of Fleiss.[6]

Table I. Distribution of abnormal outcome cases

	No. of cases	*%*
SGA (weight <10th percentile)	43	39.4
Apgar at 5 minutes <7	9	8.3
Umbilical artery pH <7.2	13	11.9
Fetal distress	36	33.0
Meconium	52	47.7
Neonatal intensive care unit admission	5	4.6
Total abnormal outcomes	109*	

*An individual case might have one or more abnormal outcomes.

Results

Of the 350 cases, 109 (28%) pregnancies culminated in adverse outcomes. The distribution of various ad-

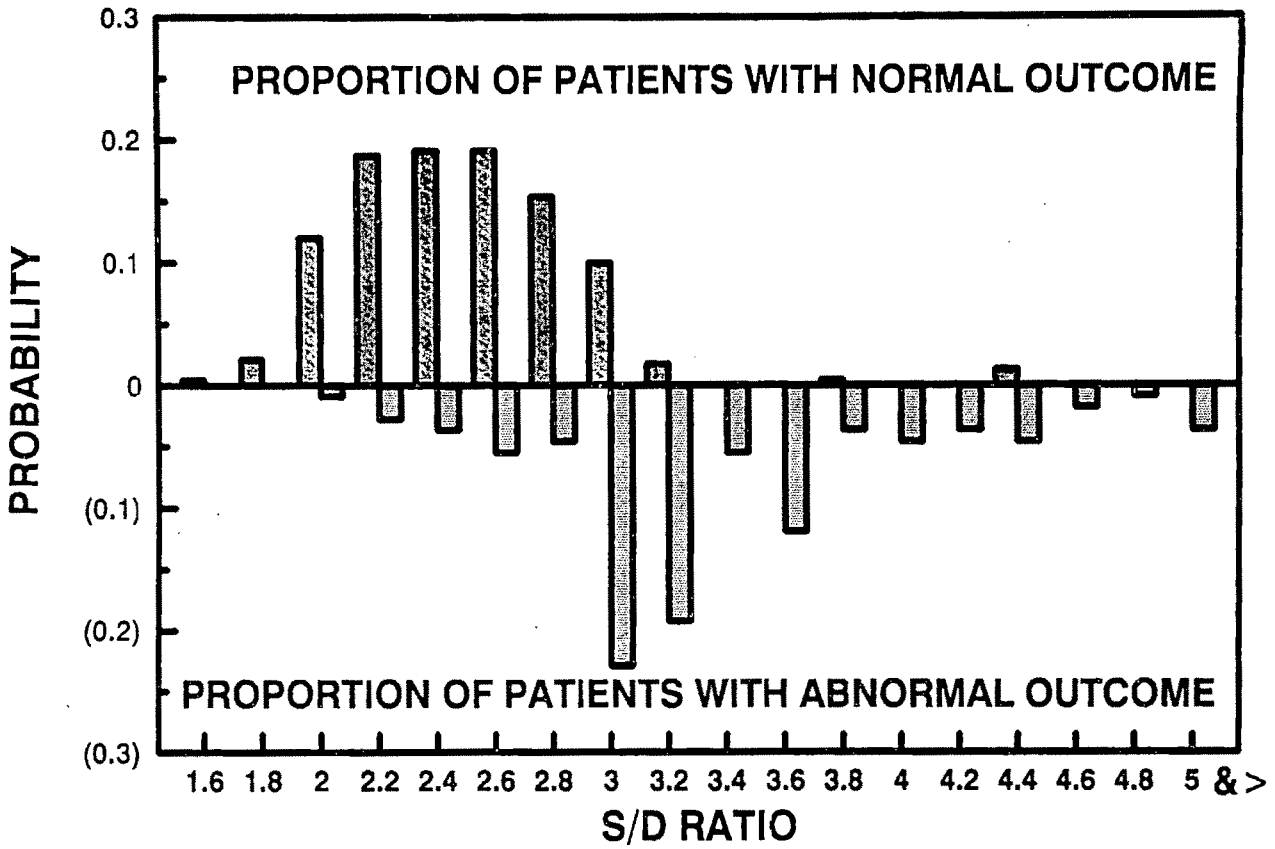


Fig. 2. The distribution of the umbilical arterial systolic/diastolic ratio among patients with and without normal perinatal outcome. Each vertical bar above the zero line represents the proportion of the total normal patients at a given systolic/diastolic ratio value; the *bars* below the zero line represent the same in the abnormal population. Note that the systolic/diastolic ratio cutoff values are capable of discriminating the patients with differing probabilities of normal and abnormal perinatal outcomes. However, no cutoff value designates all patients with adverse outcome as test positive without falsely categorizing some patients with normal outcome as test positive.

Table II. Test performance values for various systolic/diastolic ratio cutoff points

Cutoff point	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Kappa index*
2.5	0.93	0.53	0.47	0.94	0.36
2.9	0.83	0.87	0.74	0.92	0.68
3.0	0.79	0.93	0.83	0.91	0.73
3.5	0.35	0.99	0.93	0.77	0.41

Table III. Diagnostic efficacy of systolic/diastolic ratio cutoff point of 3.0 to predict the various abnormal outcomes

Category	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Kappa index*
General abnormal outcome	0.79	0.93	0.83	0.91	0.73
SGA only	0.75	0.77	0.32	0.95	0.33
FD, Apgar, pH, NICU	0.86	0.88	0.68	0.96	0.69
FD, Apgar, pH, NICU, and meconium	0.82	0.92	0.81	0.92	0.74

FD, Fetal distress; *NICU,* neonatal intensive care unit admission.

verse outcome parameters is shown in Table I. It should be noted that an individual pregnancy might have more than one abnormal outcome. In the normal outcome group, the mean (±SD) birth weight and gestational age were 3295.5 (±475) gm and 39.1 (±1.5) weeks, respectively; in the abnormal group, the corresponding figures were 2817.3 ± gm and 38.0 (±2.3) weeks, respectively. The cesarean section rates for the normal and the abnormal groups were 17% (43/241) and 35% (38/109), respectively. Fig. 1 depicts the frequency distribution of the systolic/diastolic ratio. As expected, this distribution was not Gaussian. The probability density distribution of systolic/diastolic ratio among patients with normal and abnormal perinatal outcomes are shown in Fig. 2. The graph shows the separation of these two patient populations at different values of systolic/diastolic ratios; each bar at a given value of systolic/diastolic ratio represents the proportion of the total group (normal or abnormal) at that value. The receiver operating characteristic curve of the systolic/diastolic ratio is depicted in Fig. 3. By evaluating the various cutoff points of the systolic/diastolic ratio, it was apparent that the value of 2.9, and not 3.0, offered the best inherent discriminatory power. The diagnostic efficacy of systolic/diastolic ratio values of 2.5, 2.9, 3.0, and 3.5 were then further assessed by estimating the corresponding specificity, sensitivity, positive predictive value, negative predictive value, and kappa index (Table II). The results demonstrated that in the study population, an systolic/diastolic ratio cutoff point of 2.9 rather than 3.0 offered a better sensitivity but a lesser specificity and positive predictive value in regard to predicting the overall adverse perinatal outcome. According to the recommended interpretation of kappa index,[7] both 2.9 and 3.0 fared as good to excellent tests, and 2.5 and 3.5 as poor tests. The diagnostic efficacy of the systolic/diastolic ratios of 2.9 and 3.0 were then further analyzed in relation to the following subgroups of adverse perinatal outcomes: SGA only; intrapartum fetal distress, Apgar score <7 at 5 minutes, umbilical arterial pH below 7.20, and neonatal intensive care unit admission; and the latter outcomes combined with the presence of significant meconium (Tables III and IV). This analysis indicated that the systolic/diastolic ratio at both the cutoff values was a better predictor of general adverse perinatal outcome than of the suboptimal fetal growth.

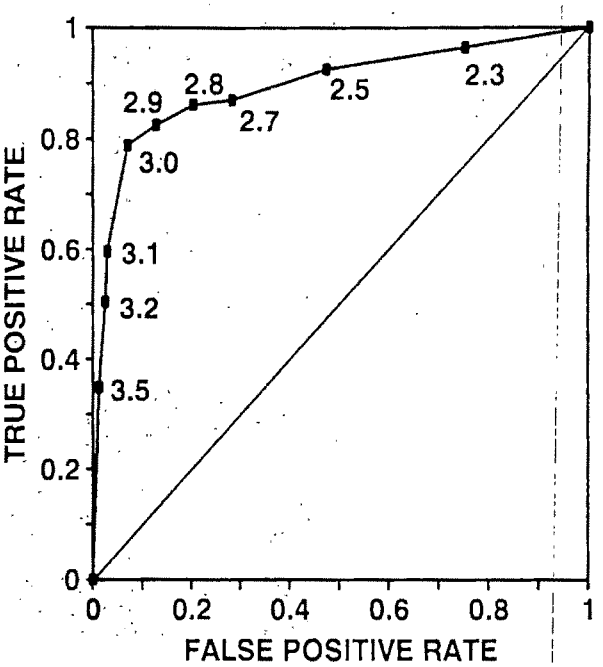


Fig. 3. Receiver operative characteristic curve of the umbilical arterial systolic/diastolic ratio. Note the systolic/diastolic ratio cutoff point (2.9) closest to the upper left corner of the graph possesses the best ability to discriminate between the normal and abnormal perinatal outcome groups.

Comment

Antepartum recognition of pregnancies with an elevated risk of adverse perinatal outcome continues to be a major challenge in obstetric practice. A significant proportion of infants who are recognized as being at low risk by the existing criteria of risk assessment experience a compromised outcome. Existing fetal monitoring techniques are only used in pregnancies already identified as high risk. Currently, maternal assessment of fetal movement on a daily basis offers the only screening tool for all pregnancies. It is in this context that the need to explore the potential of umbilical arterial Doppler velocimetry as a screening tool can be appreciated, especially because this test can be performed simply and readily with a relatively inexpensive continuous-wave Doppler device.

Earlier studies had established the feasibility of using Doppler ultrasonographic technology in assessing blood flow velocity in the umbilical artery.[8-10] Subsequent experience demonstrated a significant association between an abnormal Doppler index and pregnancy complications.[11, 12] More recently several preliminary studies have indicated that the umbilical arterial Doppler velocimetry can be a powerful predictor of an adverse perinatal outcome.[13-15]

Consistent with the principles stated previously for the essential evaluatory steps in developing a diagnostic test, this component of our ongoing project aimed to assess comprehensively not only the diagnostic efficacy, but also the various cutoff points of the systolic/diastolic ratio. The latter is a critical component of the assessment process since the diagnostic efficacy of the test is also dependent on the choice of the cutoff point. In this regard the probability distribution graph of the normal and abnormal outcomes at the various sys-

Table IV. Diagnostic efficacy of systolic/diastolic ratio cutoff point of 2.9 to predict the various abnormal outcomes

Category	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Kappa index*
General abnormal outcome	0.83	0.87	0.74	0.92	0.68
SGA only	0.75	0.71	0.27	0.95	0.23
FD, Apgar, pH, NICU	0.86	0.82	0.60	0.96	0.56
FD, Apgar, pH, NICU, and meconium	0.86	0.83	0.66	0.89	0.57

FD, Fetal distress; *NICU*, neonatal intensive care unit admission.

tolic/diastolic ratio cutoff points (Fig. 2) and the receiver operating characteristic curve (Fig. 3) immensely facilitated an objective determination of the most appropriate test value. Subsequent assessment of the test value was assisted by the determination of not only the traditional parameters such as the sensitivity, specificity, and positive and negative predictive values, but also the kappa index.

It should be noted that our study population with a 30% abnormal perinatal outcome cannot be considered a low-risk general obstetric population. This is not surprising because most patients were medically indigent and therefore were at high risk for a multiplicity of medical and social problems. Given this specific population background, our investigation suggests that extreme values such as 2.5 and 3.5 may not be suitable for clinical application. Furthermore, the cutoff values of 2.9 and 3.0 demonstrated impressive diagnostic efficacy. However, the commonly used cutoff value of 3.0 demonstrated a higher specificity, positive predictive value, and kappa index than those related to the value of 2.9. In view of the inherent imprecision of the method as demonstrated by the interobserver and intraobserver variations,[1] such apparently subtle differences in the cutoff point may not be clinically meaningful. It was interesting to note that the ability of the systolic/diastolic ratio (at cutoff values of 2.9 and 3.0) to predict only SGA was inferior to its ability to predict other adverse outcome parameters. Exclusion of the presence of thick meconium as an adverse outcome parameter improved sensitivity, but reduced the specificity, positive predictive value, and the kappa index.

In the final analysis the choice of the systolic/diastolic ratio cutoff point should consider the prevalence of the disease and other factors contributing toward its probability of occurrence before the test; thus in a low-risk population with a lower prior probability of abnormal outcomes, this test threshhold value will not demonstrate the same degree of high predictive value. In selecting the cutoff values, it would also be necessary to consider the consequences of a false-positive diagnosis against those of a false-negative diagnosis, particularly in regard to the use of the test as a screening tool as opposed to its use as a confirmatory diagnostic method. Furthermore, any comprehensive clinical assessment of the umbilical arterial Doppler velocimetry should encompass evaluating the relative merits of the various techniques of waveform analysis, and testing their diagnostic efficacy in conjunction with the existing standards of practice for fetal surveillance.

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Table I. Studies of umbilical artery Doppler velocities and fetal outcome

Report and year	*No. at high risk*	*Criteria*	*Cutoff*	*SN*	*SP*	*PPV*	*NPV*
Maulik et al.[2] (1989)	350	IUGR 5 min Apgar score <7 art. pH <7.25 thick meconium fetal distress NICU	3.0	79	93	83	91
Fleischer et al.[9] (1985)	189/Mix	IUGR	≥3.0	78	83	49	95
Schulman et al.[10] (1989)	255/195	IUGR	≥3.0	65	91	43	96
Trudinger et al.[11] (1985)	172/172	IUGR 5 min Apgar score <7 Neonatal death	95%	64 62	77 79	55 63	83 78
Marsal et al.[12] (1987)	142/142	IUGR	±2 SD	57	85	80	64
Arduini et al.[13] (1987)	75/75	IUGR	±1 SD	61	73	50	81
Gaziano et al.[14] (1988)	256/256	IUGR	≥4.0	79	66	79	96
Divon et al.[15] (1988)	127/127	IUGR	>3.0	49	94	81	77
Berkowitz et al.[16] (1988)	168/168	IUGR	≥3.0	45	89	58	86
Al-Ghazali et al.[17] (1988)	300 + 71	IUGR	95%	72	87	82	79

IUGR, Intrauterine growth retardation; *SN,* sensitivity; *SP,* specificity; *PPV,* positive predictive value; *NPV,* negative predictive value; Art., arterial; *NICU,* neonatal intensive care unit admission.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Kathryn L. Reed, Tucson, Arizona. The extended abstract and additional tables by Maulik and colleagues detail one of the largest reported series of patients examined with Doppler ultrasonography during pregnancy. I would like to focus on three aspects of the study.

First, what does the umbilical artery waveform measure? We know that blood flow in the fetus results from a complex interaction of pressure changes, volume flow, heart rate, resistance, vessel wall elasticity, vessel size and shape, ventricular function, and blood viscosity. Thompson has stated that there is not a physical entity that can be measured that corresponds to the blood velocity waveform.[1] However, it is important to outline the various physical factors that influence the waveform, and to perform experiments in which these factors are varied.

In addition to the sources of physiologic variability, there is also potential variation in the measurement of the waveform itself. Estimates of error inherent in the waveform measurement range from 4% to 10%.[2,3] This amount of error would make the distinction between 2.9 and 3.0 clinically irrelevant.

Second, why were the particular end points chosen with which the changes in Doppler waveforms are compared? Endpoints are notoriously elusive and difficult to quantitate, and several investigators have battled with the concept. Perinatal mortality is uncommon enough (8/1000 live births[3]) that studies in many patients are required to show improvement. For this reason, outcome variables are often directed toward measures of morbidity, particularly asphyxia. These endpoints, however, are also somewhat elusive. The definition of intrauterine growth retardation varies by geographic location; furthermore, not all fetuses with small size are abnormal.[4] An Apgar score of <7 at 5 minutes does not correlate with long-range outcome.[5] Asphyxia probably does not occur above a pH of 7.20[5] and after a normal birth the umbilical artery pH is 7.28 ± 0.05 (range, 7.15 to 7.43,[7] thus the value used in this study is actually in the normal range. Presence of meconium may or may not be associated with adverse fetal outcome; in one study 1% of neonates with meconium had true acidemia.[6] The definition of fetal distress may vary with examiner; 16% of those delivered for fetal distress had severe acidosis (umbilical artery pH <7.12) in a report by Sykes et al.[8] Admission to the neonatal intensive care unit may be more a result of the prematurity of the neonate than hypoxia or asphyxia. At times birth events may alter fetal state from

normal to abnormal. It would be unlikely that a single common pathway ("placental resistance") would account for the morbidity seen at birth.

Finally, several other investigators have reported similar studies. Table I lists nine of these studies.[9-17] The studies varied in terms of definitions of morbidity and ratio cutoff points; sensitivities ranged from 45% to 79%.

I will close with several questions for Dr. Maulik. (1) What do you think the velocity waveform measures? (2) How do you explain the association between the waveforms and the outcome variables you chose to measure? and (3) Can you explain the wide variation in results reported in other studies of umbilical blood flow velocity in pregnancy?

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Dr. Daniel A. Rightmire, Springfield, Illinois. I would like to ask Dr. Maulik what the interval was from the time of systolic/diastolic measurement to delivery in the normal and abnormal outcome pregnancies. By testing at 36 weeks, many of the very high-risk pregnancies may have been eliminated from consideration.

The authors' use of the frequency distribution curve format for presentation of their data is highly informative. We see from Fig. 1 and Fig. 2 that the distribution curve for the systolic/diastolic ratio is non-Gaussian. The distribution curve for patients with an abnormal outcome is especially skewed. It is also considerably expanded compared with the curve for normal patients. Thus the authors were wise to use distribution-independent statistical techniques. Descriptive and inferential statistical techniques that depend on normally distributed data and equal variances in tested populations such as *t* tests, certain analyses of variance, and linear regression techniques are inappropriate for use with systolic/diastolic ratios. The systolic/diastolic ratio can be corrected for nonnormality of the underlying distribution by transforming from the Pourcelot ratio values.[1,2]

Although the authors stress the different performance of systolic/diastolic at a cutoff of 2.9 versus 3.0, we are aware that with about 9% variability in the measurement technique, a value of 2.9 is probably indistinguishable from 3.0 when actual measurements are made. Test results such as 2.7, 3.0, and 3.3 might represent discernible steps with the continuous-wave Doppler technique.

In Table III the data are displayed that indicate that the systolic/diastolic ratio is not a particularly good predictor of a small fetus. This is not really unexpected because some fetuses are constitutionally small and do not suffer from a placental lesion or hypoxia.

Whereas the sensitivity and specificity of a test are properties of the test itself and of the outcome parameters chosen, the predictive value of a positive test is influenced greatly by the prevalence of disease in the study population. For a sensitivity of approximately 80% and a specificity of about 90% with a prior probability of 31% for an adverse outcome, the predictive value of a positive test will be approximately 70% to 80%. However, if the same test is used in a low-risk population with, for example, a prior probability of 5% to 10%, then the positive predictive value declines to approximately 30%.[3] Thus the performance of the systolic/diastolic ratio in a low-risk population has yet to be characterized and might be predicted to be rather poor.

Dr. Maulik has defined and studied the systolic/di-

astolic ratio as a test. He has characterized a cutoff value at about the 90th percentile of the normal population. However, I would like to ask Dr. Maulik if we should not consider the systolic/diastolic ratio as a test but rather as an examination. Are we not listening to the fetal umbilical circulation in an attempt to diagnose an underlying placental lesion definable histologically as an obliteration of medium-sized arteries?[4]

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DR. JOHN A. GARBACIAK, JR., Phoenix, Arizona. Dr. Maulik, in your 350 patients, did you measure the umbilical blood flow at a specific point in the umbilical cord in all of these patients or did you measure it in a variety of places, placenta, fetus, and midcord? Are these values averages of those measurements?

DR. WASHINGTON HILL, Omaha, Nebraska. My question regard any information Dr. Maulik has with regard to a cutoff at an earlier gestational age, for example 30 weeks? Do you have any information you can share with us about that?

DR. MAULIK (Closing). Dr. Reed's question: "What does the Doppler index measure?" addresses a complex issue. The Doppler technique assesses the velocity waveform—this is the fundamental point. What controls the velocity waveform? Theoretically, both proximal and distal circulatory factors. Provided the central circulatory parameters such as the heart rate and cardiac contractility remain constant, the waveform reflects what is happening in the downstream circulation. There are studies (both in vitro and in vivo in animal models) that have correlated the waveform changes with the input impedance or the peripheral resistance of the downstream circulation. Obviously, in any interpretations of the Doppler indices, one needs to assume that the other factors in the circulation are constant.

In relation to the choice of the outcome parameters, I would like some guidance regarding what other kinds of morbidity parameters that we could choose. We do not claim any originality in our choice of these parameters. We followed the path taken by various investigators, such as those who had evaluated the nonstress test, contraction stress test, biophysical profile, and Doppler indices. This question has been debated, and I acknowledge freely that these are not perfect criteria.

Small for gestational age is probably a better terminology for what I described in the abstract as intrauterine growth retardation. That is why I presented this parameter in the paper as SGA. As pointed out by Dr. Rightmire, this condition is a "mixed bag." It is not surprising that the test did not predict SGA well.

We acknowledge that the presence of meconium is a soft criterion for adverse outcomes. We used our existing standard of practice, imperfect as it might be. The primary point is that in our experience, the inclusion or exclusion of this parameter did not make any difference in the results. In relation to the umbilical cord arterial pH threshhold value, I believe this was discussed previously in relation to another presentation. We abided by the current institutional standard. It is a controversial area, and 7.15 probably would be a better cutoff point.

I can only speculate in relation to variations in the reported specificity results. I believe the specific techniques used in the various studies may affect specificity. Moreover, population characteristics can certainly influence the variance. For example, characteristics of the patients enrolled in the Doppler study in Long Island would probably not be the same as patients we would encounter in Truman Medical Center, which serves the downtown indigent population.

I agree that the difference between the cutoff points of 2.9 and 3.0 is probably inconsequential given the error inherent in the technique. Actually, if we have to accept the validity of the kappa index, 3.0 is better than 2.9.

In relation to Dr. Rightmire's comments, he raises a philosophical question that I profess an inability to answer. We probably need to develop a test to differentiate between a test and an examination! Whatever we do with the patient ultimately translates into some kind of action. What practical difference does it make if we define this test as an examination or as a test? If you would recall, Dr. Schulman recently made a presentation on this isue. I believe that if the Doppler index is a test, let us call it a test, evaluate it as a test; and if it is indeed valid, then we should use it as a test. Otherwise, we should not.

In relation to the question of the applicability or validity of our results to an earlier gestational age, I think the results that we have are probably valid up to 28 to 30 weeks. Again, we have not presented here the results specifically in relation to earlier gestational ages, but on the basis of the published results and from our own experience, I believe we could use the same cutoff values up to 30 weeks' gestation.

With regard to the exact source from which we took these samples, we used a continuous-wave Doppler device and therefore used an inherently blind technique. That is probably the way we believe that this technique may be translated into a mass screening test. There are abundant data in the literature to demonstrate the validity of the continuous-wave Doppler approach. However, I would like to refer to our presentation at the Central Society meeting last year. The location of the measurement, specifically the abdominal end versus the placental end of the cord, can contribute 29% to 46% of the variance of the Doppler indices. Thank you.

Surgical management of breast disease in an obstetrics and gynecology group

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The surgical management of breast disease from 1978 through 1988 by the Women's Health Center of Logansport is reviewed. Three hundred twelve biopsy procedures resulted in the diagnosis of 59 cancers. Biopsy and mastectomy procedures were performed by the authors (obstetrician-gynecologists). There were no significant complications and all patients had an adequate surgical result. Preoperative needle localization techniques proved to be a safe and effective method to identify and remove nonpalpable mammographic abnormalities. Because women depend on their gynecologist for advice regarding reproductive organs including the breasts, it is logical for the gynecologic surgeon to become involved in the surgical management of breast disease. (AM J OBSTET GYNECOL 1990;162:1526-34.)

Key words: Breast disease, mammography

Breast cancer is the most common malignancy among women in most of Europe, North America, Latin America, and Australia. As many as one in 10 women in the United States may suffer from breast cancer during her lifetime. Breast cancer is also the second leading cause of cancer deaths in the United States, accounting for 18% of all female cancer deaths.[1] The obstetrician-gynecologist has a responsibility to patients to provide the latest and most accurate information regarding breast disease. Because the gynecologist holds the unique position as a primary care physician whom women consult with regard to breast disease and as a surgical specialist, the obstetrician-gynecologist can offer both diagnostic and definitive surgical treatment. Since early diagnosis is the key to breast cancer survival, the patient's primary care physician must aggressively search for early breast carcinomas. By participating in the management of the disease, the gynecologist will become a better diagnostician and better serve his or her patients. This article reports the surgical experience of an obstetric-gynecology group with breast disease from 1978 through 1988.

Material and methods

Two hundred and eighty-one patients seen from 1978 through 1988 had surgical procedures involving the breast performed by members of the Women's Health Center of Logansport. Author B. R. H. founded the practice in 1948; J. A. H. joined in 1978; and D. C. M. joined in 1982. B. R. H., J. A. H., and D. C. M. performed the biopsy procedures. B. R. H. and J. A. H. performed the mastectomy or breast conservation procedures. Mammography was provided by the local hospital radiology group and in most situations was reviewed by members of our group. Needle localizations before biopsy of abnormal mammographic areas were done by the radiology group. Training in breast surgery was gained either as part of residency training or by association with practicing breast surgeons. Patients were encouraged to have screening mammograms according to American Cancer Society guidelines.

Results

Three hundred and twelve biopsy procedures of 212 patients were performed; 157 involved the right breast and 155 involved the left breast. Sixteen bilateral procedures were performed. Of the patients who had operations because of a palpable mass, two thirds were detected initially by the patient and one third by the physician on screening examination. Two hundred and seventy-three of the procedures were done with the patient under general anesthesia and 31 with local anesthesia. Ninety-one needle localization biopsy procedures were performed for mammographic abnormalities. Of these 91 procedures, 62 were done for calcified abnormalities. In 61 of the 62 lesions with calcified abnormalities, specimen radiography confirmed the abnormal area had been removed with the initial biopsy attempt. One patient returned for a second excisional biopsy and the area was successfully removed. Confir-

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mation of successful removal of noncalcified lesions (29 patients) was established in all patients by postbiopsy mammography. Therefore the rate of successful removal with the initial excisional biopsy for abnormal mammography was 99% (90 of 91 patients). Fifty patients who had operations for a mass also had a mammogram suggestive of malignancy. Thirty-three of these 50 biopsy procedures revealed carcinoma. One hundred eleven patients had operations for a mass and had a negative mammogram at the same time. Of these 111 patients, 11 had carcinoma in spite of their negative mammogram. The histologic findings of the biopsy specimens are revealed in Table I. There were 59 breast carcinomas confirmed by biopsy.

Table II shows the age distribution of patients undergoing breast biopsy procedures.

Table III provides year-by-year summation of the biopsy procedures. This table summarizes the percentage of biopsies with malignant histology for each indication during each year. Of 214 patients who had operations for breast mass, 50 (23%) had cancer. Nine of the 91 (10%) of the patients who had operations for mammographic abnormalities had cancer. However, since 1985 nine of 63 (14%) patients who had operations for mammographic abnormalities were found to have cancer. The fact that none of the mammographic abnormalities led to a diagnosis of breast cancer before 1985 is not totally unexpected because of the relatively recent use of the mammogram protocol procedures. As time progressed, both surgeons and radiologists gained confidence in what types of abnormalities should have biopsies performed. None of the patients who had biopsy specimens taken for pathologic nipple discharge in the absence of a mass have had carcinoma. Of all patients who had biopsies for any indication, 19% were found to have breast cancer.

Because patients diagnosed with cancer before the discovery of a mass have a better prognosis, the cancer patients have been divided into those discovered with a palpable mass and those discovered by mammographic abnormality alone (occult or T0 lesion). Of those cancers in the palpable mass group (50), there were 23 right breast cancers and 27 left breast cancers. The patient discoverd the mass in 37 of the 50 cancer patients, and in 13 the mass was found by the physician at the time of routine examination. Of the patients with breast cancer, some had other malignancies including prior breast cancer (three cases), lung cancer (one case), carcinoma in situ of the cervix (two cases), and adenocarcinoma of the endometrium (two cases). Only three of the 40 patients who had a recorded family history had a positive family history for breast cancer involving their mother or sister. Thirty-seven of the 50 patients with cancer with a palpable mass were initially seen with stage I cancer by the TNM method. Eight

Table I. Principal diagnosis of 312 breast biopsy procedures

Histologic findings	*No. of patients*
Fibrocystic disease	180
Cancer	59
Fibroadenoma	49
Sclerosing adenosis	12
Fibrosis	5
Intraductal papilloma	4
Fat necrosis	3

patients had stage II lesions, none had stage III disease, and one had stage IV cancer. Nine of the 50 patients with cancer with a palpable mass were gravida 0, two were gravida 1, and 39 were gravida 2 or more.

Table IV summarizes the status of lymph nodes as well as estrogen and progesterone receptors at the time of biopsy diagnosis for the palpable mass group and the group in which the cancer was suggested by mammographic abnormality alone. The palpable mass group has been subdivided into whether the patient or physician first discovered the mass. Of all patients with a palpable mass, 41% had malignant axillary nodes and 13% had four or more malignant nodes. Histologic features of the palpable cancer group revealed 45 ductal carcinomas, three medullary carcinomas, one ductal carcinoma in situ, and one inflammatory carcinoma. Treatment in this group primarily consisted of modified radical mastectomy. Eleven patients in this group received postoperative chemotherapy and 16 received hormonal treatment with tamoxifen. There were no significant surgical complications, such as excessive blood loss or infection. None of the patients required skin grafting. Two of the patients refused therapy and the axillary dissection was not done in two others. One of these patients had metastatic disease initially and died shortly thereafter. The other, more than 80 years old, had bilateral breast cancer with significant medical problems; unilateral modified radical mastectomy was done and segmental mastectomy was done on the opposite side. Of the 50 patients in the palpable cancer group, nine chose to have mastectomies performed by other surgeons. This number is not surprising because of the extreme emotional overlay of this disease. Patients with breast cancer often seek multiple physicians' opinions. The adequacy of the axillary dissection performed by members of our group compared with the patients who had operations elsewhere is documented by the fact that the nodal count of patients whose operations were performed elsewhere averaged 17 and the axillary nodal count of those whose operations were done by members of our group averaged 16 nodes removed.

Nine patients had breast cancer suggested by mammographic abnormality alone; four cases involved the

Table II. Age distribution of patients undergoing breast biopsy procedures

Age (yr)	*Total No. of biopsy procedures*	*Biopsy specimens with benign histologic findings*	*Biopsy specimens with malignant histologic findings*
<30	30	28	2
31-40	61	53	8
41-50	103	89	14
51-60	50	39	11
61-70	43	25	18
71-80	8	2	6
81-90	1	1	0

Table III. Indication for and results of breast biopsy procedures

	No. of malignancies found per total no. of biopsies by indication			
Year	*Palpable mass*	*Abnormal mammogram*	*Nipple discharge*	*Total*
1978	2/10	0/0	0/1	2/11
1979	2/15	0/0	0	2/15
1980	6/17	0/1	0	6/18
1981	3/15	0/2	0	3/17
1982	4/18	0/4	0/2	4/24
1983	1/17	0/3	0/1	1/21
1984	6/25	0/18	0/1	6/44
1985	8/26	3/24	0/2	11/52
1986	5/15	1/8	0	6/23
1987	7/32	2/15	0	9/47
1988	6/24	3/16	0	9/40
TOTAL	50/214 (23%)	9/91 (10%)	0/7 (0%)	59/312 (19%)

right breast and five involved the left breast. Eight of nine of these patients were gravida II or more and only one was gravida 0. Two of the nine patients had a positive family history for breast cancer and seven had no breast cancer in the family. All nine patients were first seen with a stage I T0 lesion (occult). After biopsy, surgical treatment consisted of modified radical mastectomy or segmental mastectomy, axillary node dissection, and radiotherapy. Malignant axillary nodal count is summarized in Table IV. Eight of the nine patients had negative nodes. One patient had two positive nodes. This patient was under 40 years of age and had a prior breast cancer on the contralateral side with known metastatic disease; however, she desired mastectomy. One patient's tumor was too small to measure hormone receptor volume. Two of the patients were treated with tamoxifen and two received chemotherapy. The pathology report revealed invasive ductal carcinoma in all nine patients. As with the group diagnosed with a palpable mass, patients often seek second opinions in response to the fear established by this disease. After biopsy, two of the nine patients with cancer had operations elsewhere; the number of axillary nodes removed averaged 11. The adequacy of the axillary dissection by members of our group was confirmed because the nodal count removed averaged 13.

Fifty-two of the fifty-nine patients with breast cancer, chose modified radical mastectomy, whereas three chose a conservation procedure of segmental mastectomy with axillary node dissection and radiotherapy. Four patients did not have a mastectomy or any definitive surgical therapy. As discussed previously, two of these patients refused therapy, thus attesting to the psychologic impact of this disease. One of the patients who refused therapy had metastatic disease that developed shortly thereafter and she died. Two patients were not treated because of metastatic disease or age and general medical condition.

Of all patients undergoing breast biopsy procedures by our group, none have had any significant complications. None of the patients had reoperations for complications and none had any significant infection. None of the mastectomy group had any significant complications. There have been no extended hospital stays, and the cosmetic results of surgery were satisfactory. None of the patients required postmastectomy skin grafting.

Comment

It has been documented by the results over the past 11 years that the obstetrician-gynecologist has the surgical expertise to manage breast disease. As practice

Table IV. Axillary node metastasis and hormone receptors related to cancer discovery

	Patient-discovered mass (No. of patients)	*Physician-discovered mass (No. of patients)*	*Abnormal mammogram (No. of patients)*
No. of malignant axillary nodes			
0	22	6	8
1	5	2	0
2	2	2	1
3	1	0	0
≥4	3	3	0
Total no. of patients with known nodal count	33	13	9
Hormone receptor status			
Estrogen and progesterone positive	14	7	4
Estrogen and progesterone negative	9	4	2
Estrogen positive, progesterone negative	4	1	2
Estrogen negative, progesterone positive	1	0	0
Total no. of patients with known receptor status	28	12	8

trends point to more breast conservation procedures, the surgical treatment becomes less complex. Radical mastectomy with complete axillary node dissection is no longer the standard of care. The number of breast cancers discovered over the past 11 years resulted from aggressive investigation for breast disease and encouraging patients to become involved in breast surveillance. None of the patients in this group had any significant complications. All patients who had operations for a palpable mass had the mass successfully removed with the initial biopsy procedure. Of the patients who had operations for mammographic abnormality with the aid of needle localization, 90 of the 91 (99%) had that abnormality removed with the first attempt. In the one patient who required second surgery, the needle placement was not in the area of the abnormality. In retrospect, this patient's abnormality represented a calcified area some years after a steering wheel injury to the pectoralis major muscle and the abnormality was not within the breast. However, this area was removed with the second needle localization attempt. This rate of successful biopsy of mammographic abnormal areas is compatible with studies by Ostrow et al.[2] and Leis et al.[3] These reports indicated that 2.7% and 2% of patients required a second excisional biopsy procedure to remove the abnormal mammographic area. Norton et al.[4] reported successful removal of the target lesion in 92% of patients who had general anesthesia and only 78% of patients whose biopsies were performed with use of local anesthesia. In this study over the past 4 years, 14% (nine of 63) biopsies for abnormal mammograms led to a diagnosis of cancer. This also is compatible with published reports by Ostrow et al.[2] (12.4%), Poole et al.[5] (14%), and Wright (9.8%). Leis et al.[3] and Schwartz et al.[7] have reported a higher rate of malignancy discovered from abnormal mammography at 38.2% and 32%, respectively. Eight of the nine patients with cancer suggested by abnormal mammogram alone had negative axillary nodes, and this is similar to the report by Rosenberg et al.,[8] who reported that all their patients with occult breast lesions had negative nodes. Poole et al.[5] reported that 17% of study patients with occult cancer discovered by mammography had axillary nodal metastasis. In contrast, 41% of those patients in this study whose cancer was initially detected as a palpable mass were found to have malignant axillary nodes and 13% had at least four malignant nodes.

The significance of receptor assays to prognosis has been somewhat controversial.[9] However, many feel that positive receptor status implies a better prognosis.[10] Of the patients whose breast cancer was discovered with a palpable mass, 40 had estrogen receptor studies performed. Fourteen of these 40 patients (35%) had negative estrogen receptors. In the group whose lesions were discovered by mammogram, two of the eight (25%) had negative estrogen receptors. In the palpable mass group, 18 of 40 (45%) patients had negative progesterone receptor assays and four of eight (50%) had negative progesterone receptors among the group with lesions discovered on mammogram. Although receptors status does not appear significantly different between the palpable mass group and the group with lesions detected by mammogram, it is noteworthy that the mammogram group had a much lower incidence of malignant axillary nodal involvement.

The numbers of patients in this report are too small to provide meaningful discussion with regard to outcome. Treatment protocols with chemotherapy have changed over the years. Thus it is not possible to compare patients and their survival. However, published reports indicate that patients with negative nodal status have a better chance of survival, as perhaps do those with positive estrogen and progesterone receptor assays. Thus it may be presumed that patients in this

group with diagnosis in an earlier stage of the disease with negative nodal involvement will have an improved chance of survival. In this report, 46 patients with cancer diagnosed with a palpable mass have recorded follow-up of 1 to 11 years. The majority of recurrences and deaths occurred within 5 years of the initial diagnosis. However, there was one patient who developed metastatic disease 9 years after mastectomy. Two of the patients died within 1 year of operation. There was additional death at 2 years. Two patients died at 3 years after operation and another died at 4 years. Thus six patients in the palpable mass group died of breast cancer within 5 years of diagnosis. Two patients also died of other causes and two had metastatic disease within 5 years and have been lost to follow-up. Nine of the 46 (20%) patients with follow-up and a palpable mass at diagnosis have died from the disease or have metastatic disease.

Of the patients whose disease was discovered by mammographic abnormalities, follow-up ranges from 1 to 4 years. None of those patients has had metastatic disease or has died of disease. One patient has died, but this is thought to be a result of the metastatic disease from the contralateral breast.

Patients whose breast cancer is diagnosed with a palpable mass have a worse prognosis and outcome than those suggested by mammographic abnormality alone. Leis et al.[3] reported a 10-year survival for those patients with occult lesions of 96.2% compared with 73% for those with stage I cancers and 43.1% for those with stage II cancers. Eleven patients with cancer were diagnosed with a palpable mass and had a negative mammogram concurrently. This emphasizes the absolute necessity of realizing that a mammogram is *not* a substitute for biopsy. It has been reported by Edeiken[11] that 22% of patients with palpable carcinoma had a negative mammogram, confirming the need to consider breast palpation and mammography as complementary procedures. It was also found that not all patients with a palpable mass suggested mammographically to be malignant actually had cancer. Family history proved to be of little prognostic significance because only five of 49 patients with breast cancer with recorded family history had a first-degree relative with breast cancer.

Breast cancer is a common malignancy with which the practicing obstetrician-gynecologist must become familiar. It is in the best interest of our patients that aggressive screening be used to ensure early diagnosis. Modified radical mastectomy and segmental mastectomy with axillary node dissection are within the surgical skills of the gynecologic surgeon. Our involvement in breast disease heightens both the patient's and our own awareness of the need for aggressive diagnostic screening. As more patients have mammographic examinations, increased numbers of abnormal areas will require biopsy procedures. It is not in our best interest to send our patients to others for biopsy procedures. Needle localization technique is safe and accurate and offers an excellent opportunity to adequately investigate mammographic abnormalities. Unfortunately, only approximately 10% to 15% of American women over the age of 50 have ever had a mammogram.[12] It is the responsibility of the obstetrician-gynecologist to encourage physicians and patients to use mammographic screening.

Three hundred and twelve biopsy procedures in this study resulted in the discovery of 59 breast carcinomas. Ninety-one biopsy procedures were for nonpalpable mammographic abnormalities leading to the discovery of nine breast cancers. None of the patients undergoing biopsy procedure or modified radical mastectomy by members of our group had a significant complication. Surgical management of breast disease is within the scope of expertise of the obstetrician-gynecologist and should be encouraged to better serve patients. Educational programs in breast surgery should be established.

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Discussion

DR. RAYMOND A. LEE, Rochester, Minnesota. I wish to review this presentation from two different perspectives. From the scientific perspective, this study does not advance our knowledge of diagnosis, management, or the natural history of carcinoma of the breast. The anecdotal review of a relatively small number of patients, not prospectively randomized, seen

over a 10-year period does not lend itself to a statistical review nor can we make useful comment in evaluating the survival data. However, from the clinical perspective, it demonstrates that a small group of well-trained and conscientious physicians can provide excellent primary care for patients with breast disease.

Early breast carcinoma can be subtle and easily missed on examination, by mammography, or both, only to be blatantly obvious the following year when the patient has a distorted breast, obviously the result of malignancy which, in retrospect, could be identified on the prior mammogram. Some physicians may wish to perform the appropriate examination, obtain a mammogram, and refer all patients with any abnormality to a breast surgeon. Other physicians may wish to carry out the total care of the patient with breast disease. How this care can and should be provided will depend on the circumstances of the physician's local community.

If an abnormality is identified, the physician should have a thorough knowledge of breast disease, be able to choose the appropriate diagnostic procedures, and be familiar with the alternatives in managing the problem. If a definable mass is present, then a properly performed, appropriate aspiration or excisional biopsy procedure will readily lead to a diagnosis.

It is increasingly apparent that we are confronted with patients whose breast examination may be difficult. Abnormalities consisting of fine stippling of calcification or other radiologically identifiable masses require preoperative needle placement for accurate location to aid in and ensure appropriate resection. There are several aspects that have potential pitfalls under these circumstances: (1) proper placement of the incision to permit a satisfactory cosmetic result if the mass is benign and yet to permit wide local resection or mastectomy if required; (2) confirmation that the biopsy specimen includes the abnormality noted on examination or mammography (we prefer specimen radiography to compare with the preoperative mammogram); (3) certainty that there are no other abnormalities at the biopsy site.

The pathologist must be provided with the appropriate tissue. I personally leave the operating room with the specimen, filet the specimen myself, have the radiographs taken of the various portions of the specimen, compare these with the preoperative mammogram, and then carry the suspect tissue to the pathologist. Once the diagnosis is confirmed, the biopsy site can be closed or, if necessary, the appropriate operative procedure is performed. Modified radical mastectomy or the infrequently performed standard radical mastectomy is not a technically difficult operation.

Contrary to the authors' opinion, it is my impression that the judgment required in specific patients to ensure adequate removal of the malignant lesion and yet tailor the operative procedure to produce a cosmetically acceptable breast that will lend itself to radiation treatment can be quite difficult. At least in my experience, I find that the ever-increasing number of small lesions makes it increasingly difficult to obtain the appropriate tissue specimen. Furthermore, it is imperative that we select properly the patients who will have wide local excision and axillary dissection to be followed by radiation therapy. Other patients should have a subcutaneous mastectomy, unilateral or bilateral, with immediate or delayed implants inserted as the management of their problem. Modified radical mastectomy continues to be a very important operative approach in another selected group of patients.

My point is that there is no single operation that is appropriate for all patients; instead, we need to tailor our procedure to the specific circumstances of a specific patient.

I think we can offer excellent primary care of the breast for our patients. However, with the current technical advancements the best results will be obtained when there is a coordinated team effort as has been reported in this study.

Dr. Bruce H. Drukker, East Lansing, Michigan. This study from the Women's Health Center of Logansport, Indiana, is a superb contribution to the practical gynecologic literature. It clearly demonstrates that the gynecologist not only should be involved in the care of patients with breast disease but can complete this obligation with excellence. This experience with 281 patients over a 10-year period is significant. The shrouds of "turfism" or "turf battles" were swept away and physicians were able to provide quality continuity of care for their patients. By taking the initiative and following an accepted guideline, the authors have clearly demonstrated that gynecologists, when appropriately trained, can care competently for the breast problems of their patients.

This substantial experience has demonstrated a few salient points. First, that cancer found in a palpable mass has a more severe prognosis than that diagnosed by mammography without a palpable mass. In this report 41% of patients with a palpable mass diagnosed as carcinoma had positive axillary nodes at the time of diagnosis when compared with only 12% of patients who had positive axillary nodes when a carcinoma was diagnosed only by mammographic screening. Second, an additional support of improved outcome is the observation that no patients with a mammographic diagnosis of carcinoma confirmed by biopsy and subsequently treated have had a recurrence when followed up for 1 to 4 years. This is compared with nine of 46 patients who had a palpable mass diagnosed as cancer who died or have known metastatic disease during a similar follow-up. It is important to note, however, that metastases from breast carcinoma occasionally appear later than 10 years after the initial diagnosis, but the authors clearly demonstrate that at least to date the majority of recurrences have occurred within 5 years.

Perhaps we should state that we *expect* these very positive findings. If you concur, then you also commit yourself to mandatory mammography for your patients in compliance with American College of Obstetricians and Gynecologists guidelines.

Aside from these obvious successes, however, we must examine some areas that need clarification and are of interest to us all. First, how did the group members of this practice achieve their training? Were they fortunate enough to have exposure to treatment of both benign and malignant disease of the breast in their obstetric and gynecologic residency or did they take additional formal breast training with a surgeon after completion of a residency? Perhaps the surgical exposure was more of a "preceptorship." This is a very practical question for all of us; as we look to the future and become more involved with treatment of breast disease, training is a problem. Not infrequently do I receive queries from obstetrician-gynecologists asking, "How can I learn more about surgical treatment of breast disease?" Such opportunities for obstetrician-gynecologists in the United States are quite limited. The interdigitation of this learning opportunity in residencies in obstetrics and gynecology is of extreme importance.

From a purely technical position, we should note that only 11% of the biopsy procedures were done with use of local anesthesia. Surgeons are touting the benefits of local anesthesia, the ease of the procedure, the cost-effectiveness, and the lack of inconvenience for the patient. Nevertheless, the authors suggest that the accuracy of initial biopsy is compromised by local anesthesia and they clearly quote references that suggest that the accuracy is higher when general anesthesia is used. Could the authors tell us how they discriminate with respect to the type of anesthesia they elect? This obviously has very practical implications.

The authors also fail to provide us with a critical assessment factor, which impacts all physicians involved with or making recommendations based on mammographic assessment. The question is: which nonpalpable calcifications should have biopsy and which can be followed? The authors essentially described 62 patients with calcified abnormalities who had biopsy procedures, but I could not locate a figure that stated how many of these 62 patients had a carcinoma. Radiologists have suggested that one in six or seven biopsy specimens taken because of calcifications should be malignant. If that were so, then we would expect that eight or nine patients in this group would have had malignancy diagnosed on the basis of calcification pattern alone. If the number of positive diagnoses were high, for example, 12 to 15, it would reflect a very high level of radiologic discrimination of calcifications. Conversely, if it were only two or three, this would suggest a high rate of radiologic "overcall." It is necessary to consider the impact of unnecessary biopsy procedures on the cost of medicine in general. This is a sensitive issue and one where debate, I am sure, will be ongoing for a number of years. Table III attempts to partially answer the question but does not clarify whether the abnormal mammogram included only those patients with calcifications or also those with nonpalpable or palpable masses that were interpreted to be abnormal on mammographic assessment. Clarification of this important point would be helpful.

Despite these questions, this paper clearly reconfirms that mammography is the keystone to early diagnosis of breast cancer. Although the authors report only 91 of 312 biopsy procedures done for mammographic abnormalities during the period, I would predict that the next decade will show a significant increase from the present 29% to perhaps 60% to 70% that require biopsy based on only mammographic abnormalities. This will represent a dramatic improvement and will be brought about by increasing compliance of patients with respect to obtaining mammography, increasing availability, decreasing cost, and superior mammographic technology and interpretation.

This study should clearly demonstrate the success of gynecologists and obstetricians in screening and treatment of breast cancer. I congratulate the authors for a very significant contribution.

Dr. Maurice J. Mueller, Crescent Springs, Kentucky. This article does show that gynecologists can manage breast disease, but I feel that many of us are reluctant to become involved in management of breast tumors because of the legal ramifications. It seems to add one more legally risky procedure to the other risky things that we do in our practice.

Dr. Louis Weinstein, Tucson, Arizona. Dr. Hall, have you noticed changes in breast density in mammograms of patients on a regimen of hormonal therapy? Also, a simple question, in a patient who is ≥ 3 years after the diagnosis of breast cancer with no evidence of recurrence, would you treat her with hormonal therapy if she has symptoms?

Dr. Eduard Eichner, Cleveland, Ohio. I would just like to make a comment from the "old days." I used to do biopsies of all these lesions in the office routinely without mammograms because the radiologists were just learning to do mammograms and we could never depend on the reports they gave. I found that many of the areas I aspirated, except for cysts, ended up with a small deep hematoma and a mass that becomes very suspicious on a mammogram. Therefore, since that time, I get a mammogram first, except in the case of a cyst, because apparently, by using a big needle for suction, I was producing a little blood locally that changed the picture.

Dr. Robert W. Rebar, Cincinnati, Ohio. I just have some rhetorical and philosophical questions rather than questions directed toward the authors, who clearly demonstrated that they can in their circumstances care for this group of patients.

Originally I chose obstetrics and gynecology as a clearly demarcated field, and I thought it might be possible to continue to keep abreast of all the changes in it. As we expand into ever more areas in endocrinology, perinatology, and oncology, and now in breast disease, my question is how many of us can really keep on the forefront of the changes occurring in all these different areas?

I think that this becomes a question for me as a reproductive endocrinologist when I feel overwhelmed by some of the advances occurring in other parts of our specialty without going on to suggest that we now

become cognizant and aware of a whole new area of the literature that is found in a whole different set of journals.

Dr. Hall (Closing). I think, if I gave this presentation in front of the American College of Surgeons, I probably would need a helmet and a flak jacket. I thank you for your generosity.

I think Dr. Lee had excellent points to make, and I would like to expand on one. When we do a biopsy because of a calcified abnormality, we get specimen radiography with the patient still asleep on the table. We obtain an x-ray film of the specimen and then fillet it, as he mentioned. I then take the specimen to the pathologist and show him where in the specimen the abnormality is located. This is helpful to the pathologist because the specimen often is 3 or 4 cm but the area of abnormality may only be a couple of millimeters.

It's important to help the pathologist out—to say: "Here's the spot you've got to take. You can look at all of it, but here's the one spot in particular we don't want to miss."

Dr. Drukker asked about training. Again, I was fortunate enough to go into practice with someone who trained at a time when breast surgery was within the department of obstetrics and gynecology (and that's probably one that we let get away). A lot of my training was on the job from a good teacher, and I had some association with other breast surgeons.

I think, from a philosophical standpoint, for someone who has no surgical skills and who doesn't go in the operating room on a regular basis, it's probably not a good idea. We (gynecologists) are there everyday anyway. Our lockers are in the same room as the general surgeon's. We get the same scrub suits. I think, if we can open an abdomen, certainly we can handle some aspects of breast disease.

I think we'll be better diagnosticians of breast disease if we're involved in the disease. If a patient comes in the office and has a question about her breasts and you're a triage officer, you're probably not as good a clinician as if you were involved in the disease.

Regarding questions about how to decide on local or general anesthesia, the majority of these procedures have been done with local anesthesia recently. Initially, many were done with general anesthesia. The introduction to drugs such as Versed helped tremendously as far as doing these procedures under local anesthesia. In the mammographic abnormality group we used only general anesthesia because the literature supports that, and I agree.

The patients with mammographic abnormality but without a mass are best placed under general anesthesia because the radiologists don't want the patient to lie down and have the needle placed perpendicularly because they're afraid of hitting the lung. So the patient sits up and the radiologist puts the needle in from the top down. The patient is then taken to the operating room and lies down. The tip of the needle sometimes isn't close to where you think it is; if you make an incision and try to cut down and find the tip of the needle and it isn't there and the patient is squirming on the table and wanting to know what's wrong, sometimes, as Norton found in his study, you have to abandon the procedure. We've done all procedures in patients with mammographic abnormalities under general anesthesia and have had 100% successful removal. All procedures have been done on an outpatient basis.

In the group with a palpable mass, selection of anesthesia depends on the anxiety of the patient. I ask them how do you want to do this? I prefer local anesthesia, but we let the patient become involved in that decision.

Of the group with calcified abnormality versus those with mammogram abnormalities but no calcium, I believe 63 of the 91 patients had calcium within the mammographic abnormality. I think all of the cancers were in that group. Therefore there was a discovery rate of about 16% of calcified abnormalities on mammogram that ultimately proved to be malignant, and that's right in line with the literature.

One of the questioners asked about the legal ramifications. I would cite the other side of the coin. There is ample precedent in the courtroom of malpractice in not discovering breast cancers early enough. I think, by becoming involved in the disease, you're going to find these cancers earlier, give better service to the patient, and perhaps get the medical-legal noose off your neck rather than be a triage officer whereby the patient perhaps gets lost in the system and is sent to a physician she doesn't know or maybe doesn't have confidence in. The patients already know us. They already have confidence in us, and I think we're going to do them a service and perhaps stay out of the courtroom.

I don't have any data regarding hormone effects on mammograms. Mammography is probably best not done during the menses and immediately before the menses because the breasts are too tender for compression on the mammogram. Mammography is best done the week after the menstrual period when the radiologist can compress the breast, thus using less radiation, and get a better picture. The postmenopausal breast is probably not quite in the same situation, so it probably doesn't make a lot of difference.

I have medical oncology specialists see all of these patients, so I defer to their expertise, but I would be very hesitant in putting a patient who has had breast cancer on a regimen of estrogen.

Philosophically, about one more procedure to do and one more thing to keep up on is an interesting question, with turf fights and all of that. I don't have any great pearls of wisdom about that other than I think this is something we can do. I think it's something that we dabble in anyway because the patients come in for routine breast care. They come to us with their questions, and I think it's only in their best interests that we answer those questions the best way that we can. I think the best way we can answer those questions is to become involved in the management of the disease. I don't think that's beyond our capabilities.

As far as the turf fights, battle lines for turf have

been drawn and are being drawn in hospitals and by the American College of Surgeons, which is not very happy about the gynecologist's introduction into breast disease. I hope that when the "powers that be" in obstetrics and gynecology decide who's going to champion the fight for turf in our involvement in breast disease, doers and not talkers are picked.

I think we need people who are out there seeing patients, not necessarily those who are thinking about it or postulating how to treat patients. If you're in practice and seeing patients, my recommendations make sense. This plan can work, and I think we will be doing the patient a good service.

Evaluation of a continuous combined low-dose regimen of estrogen-progestin for treatment of the menopausal patient

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Menopause constitutes a sizable proportion of the adult woman's life, and it is reasonable to consider that most women will benefit from hormone-replacement therapy. Also, it is important to realize that cardiovascular disease is a major cause of morbidity and death in the menopausal patient. Two regimens of hormone-replacement therapy were evaluated in postmenopausal women with 0.625 mg of conjugated equine estrogen with either 2.5 or 5 mg of medroxyprogesterone acetate taken continuously for 52 weeks in 92 patients. The data demonstrated an improvement in menopausal symptoms, a beneficial effect in lipoprotein profiles, the establishment of an atrophic endometrium, and a marked decrease in vaginal bleeding after 13 weeks and a further decrease after 26 weeks. Ideally this regimen will offer better patient compliance and, if the favorable lipoprotein profiles offer protection to the cardiovascular system, the overall health of the American woman will be markedly affected. (AM J OBSTET GYNECOL 1990;162: 1534-42.)

Key words: Estrogen, progestin, continuous low-dose regimen

As the population continues to age, more medical attention is being directed to quality-of-life issues. It has been reported that 90% of women live to reach menopause, with an average life expectancy of 28 years after menopause.[1] This means that the practitioner seeing female patients must have an understanding of the physiologic changes of menopause and what pharmacologic treatment is indicated.

During more than half of the average woman's life, she has the intrinsic production of hormones such as estrogen and progesterone that offer protection from cardiovascular disease and osteoporosis. After menopause the immunity from coronary artery disease and osteoporosis is lost.[2, 3] It is critical to appreciate that coronary artery disease has four times the death rate in women as breast and endometrial cancer combined.[4]

The use of estrogens for the postmenopausal patient can prevent vasomotor symptoms and urogenital atrophy and offer protection from osteoporosis.[5] If a regimen of drug administration could be determined that would offer the listed benefits, as well as protect the endometrium from carcinoma, have high patient compliance, have minimal vaginal bleeding, and alter lipid profiles favorably to decrease the risk from cardiovascular disease, the overall health of women would be vastly improved.

The regimen of a continuous low-dose estrogen-progestin combination appears to offer more benefits to the patient than does the standard sequential administration of hormones.[6] This study was devised to evaluate further a continuous regimen of 0.625 mg of

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conjugated equine estrogen with two dosages (2.5 and 5 mg) of medroxyprogesterone acetate for 52 weeks.

Patients and methods

The total population consisted of 92 women who had been menopausal for at least 1 year, had serum estradiol and follicle-stimulating hormone levels in the menopausal range, and had not received any oral estrogen or progestin for the previous month or an injectable sex hormone for the past year. The study group was not controlled for diet, alcohol use, or smoking.

After being given proper informed, written consent approved by the Human Subjects Committee of the University of Arizona and Creighton University, patients were randomly assigned from a computer-generated list of numbers to one of two treatment groups. All patients received 0.625 mg of conjugated equine estrogen (Premarin; Wyeth Ayerst, New York, N.Y.) continuously, with group I (46 patients) receiving 2.5 mg of medroxyprogesterone acetate (Provera; The Upjohn Co., Kalamazoo, Mich.) and group II (46 patients) receiving 5 mg of medroxyprogesterone acetate. Total time for the study was 52 weeks, and the treatment groups were known to the investigators.

A medical history was obtained and a complete physical and pelvic examination was performed at the initial visit. A Papanicolaou smear and endometrial biopsy were done. The endometrial histologic findings were evaluated at each individual institution. A mammogram and urinalysis were obtained. Blood work included a complete blood count, fasting serum glucose, fasting lipoprotein profile (cholesterol, triglycerides, high-density lipoproteins plus subfractions 2 and 3, low-density lipoproteins, and very-low-density lipoproteins), liver function tests, creatinine, follicle-stimulating hormone, and estradiol.

After evaluation of the baseline studies, the patients were randomly assigned by a computer-generated list of numbers to either study group. All patients were instructed in maintaining a daily diary to record any vaginal bleeding, vasomotor symptoms, or side effects.

At the end of 3 months, the patient returned for an abbreviated physical examination, diary evaluation, and repeat fasting lipoprotein profile. The same occurred at 6 months with the addition of a complete blood count, liver function tests, and fasting glucose test. The 9-month visit was identical to the 3-month visit. The 12-month visit was the same as the baseline visit, which included a complete physical and pelvic examination, mammogram, blood work including fasting lipoprotein profile, and endometrial biopsy.

Women excluded from the study were those with a hypersensitivity to either hormone preparation, abnormal endometrial biopsy or papanicolaou smear, pelvic disease, history of gynecologic cancer, hypertension, hepatic, renal, or cardiovascular disease, history of thromboembolic disease, and type I diabetes mellitus.

Serum levels of follicle-stimulating hormone and estradiol were measured with commercially available radioimmunoassay kits.

The enzymatic procedures of Allain et al.[7] and Megraw et al.[8] were used to determine total serum levels of cholesterol and triglycerides, respectively. The high-density lipoprotein cholesterol fraction was measured by a rapid-precipitation technique with a combined equal-volume mixture of 2 mol/L magnesium chloride and dextran sulfate: 0.1 ml of precipitating reagent was added to 1 ml of serum, mixed, incubated at room temperature for 10 minutes, and centrifuged for 20 minutes. A modification of the total cholesterol method was used to assay the clear supernatant for high-density lipoprotein cholesterol.[9] Low-density lipoprotein cholesterol levels were determined according to the formula of Friedewald et al.[9]: low-density lipoprotein = total cholesterol − high-density lipoprotein − 1/5 triglycerides. Very low–density lipoprotein cholesterol levels were determined by very-low-density lipoprotein = total cholesterol − high-density lipoprotein − low-density lipoprotein.

The subfraction 3 of high-density lipoprotein cholesterol was measured by precipitating the subfraction 2 from total high-density lipoprotein with dextran sulfate as described Gidez et al.[10] Subtracting subfraction 3 of high-density lipoprotein from total high-density lipoprotein resulted in the determination of subfraction 2 of high-density lipoprotein. All of the lipoprotein assays were performed at one central laboratory (The Upjohn Co.).

The results were tabulated and compared across treatment regimens by an analysis of variance technique, paired t test, and Fisher's exact test, with significance regarded at the 0.05 level.

Results

A total of 92 patients were recruited into the study. Forty-six patients were in group I, which received continuous administration of 0.625 mg of conjugated equine estrogens with 2.5 mg of medroxyprogesterone acetate, and 46 were in group II, which received the same estrogen dosage with 5 mg of medroxyprogesterone acetate for a total of 52 weeks. Thirty-one of the patients in group I and 40 of the patients in group II completed the year-long study.

The mean age of the total study group was 55.4 years, mean gravidity 3.5, and mean height 64.3 inches, with no differences noted between the groups. The mean initial weight was 150.2 pounds and the final mean weight was 151.4 pounds, with no statistical differences noted within either treatment group. Systolic blood pressure increased significantly in the total group from

Table I. Lipid levels

	Initial (mg/dl)	*Final*
Total cholesterol		
Group I	248.30 ± 46.32	240.60 ± 38.69
Group II	243.42 ± 40.36	237.26 ± 38.14
Combined population	245.57 ± 42.09	238.74 ± 37.54
High-density lipoprotein cholesterol		
Group I	54.80 ± 18.28	58.83 ± 15.66
Group II	54.55 ± 17.72	55.76 ± 13.51
Combined population	54.66 ± 15.79	57.12 ± 13.67*
High-density lipoprotein cholesterol subfraction 2		
Group I	40.77 ± 9.64	43.52 ± 8.76
Group II	40.28 ± 9.31	42.71 ± 6.93
Combined population	40.48 ± 8.64	43.05 ± 7.30
High-density lipoprotein cholesterol subfraction 3		
Group I	59.10 ± 9.77	55.16 ± 10.30
Group II	59.72 ± 9.31	57.29 ± 6.93
Combined population	59.46 ± 8.66	56.41 ± 7.79*
Low-density lipoprotein cholesterol		
Group I	166.77 ± 40.49	158.73 ± 37.96
Group II	169.76 ± 35.77	153.29 ± 36.79
Combined population	168.44 ± 36.04	155.69 ± 35.81*
Very-low–density lipoprotein cholesterol		
Group I	26.57 ± 27.05	23.17 ± 15.48
Group II	21.37 ± 16.26	26.24 ± 19.62
Combined population	23.66 ± 20.98	24.88 ± 17.53
Triglycerides		
Group I	118.13 ± 101.46	119.70 ± 85.27
Group II	107.00 ± 81.26	120.00 ± 79.52
Combined population	111.91 ± 88.72	119.87 ± 79.04

Data are means ± SD. Group I = 0.625 mg of conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate. Group II = 0.625 mg of conjugated equine estrogens plus 5.0 mg medroxyprogesterone acetate.

*$p < 0.05$.

123.5 mm Hg initially to 126.9 mm Hg at the end of the study ($p < 0.05$). Diastolic blood pressure decreased from an initial value of 76.6 to 74.3 mm Hg ($p < 0.05$). No differences were noted between the two treatment groups. Serum levels of follicle-stimulating hormone and estradiol were in the postmenopausal range.

Baseline lipid profile evaluations were similar in both treatment groups. Total serum cholesterol levels decreased 2.8% (6.8 mg/dl), although this was not statistically significant, and there were no differences between the two groups. High-density lipoprotein cholesterol levels showed a 4.5% (2.5 mg/dl) increase from the initial value to the one obtained after 52 weeks of the study ($p = 0.02$). No differences were noted between the treatment regimens. Low-density lipoprotein cholesterol levels decreased 7.6% (12.8 mg/dl) during the length of the study ($p = 0.04$), with no differences noted between the treatment regimens. The change in the low-density lipoprotein cholesterol level occurred at the end of the third month and they stayed stabile. Very low–density lipoprotein cholesterol levels increased 5.2% (1.2 mg/dl), although this change was not statistically significant in either treatment group or the total population. Subfraction 2 of the high-density lipoprotein cholesterol level increased by 6.3% (2.6 mg/dl) in the entire group, but this was not statistically significant and there were no differences noted between the groups. Subfraction 3 of high-density lipoprotein cholesterol levels demonstrated a statistically significant decrease of 5.1% (3.0 mg/dl) during the course of the study ($p = 0.04$), with no differences noted between the groups. The changes noted occurred at the end of the third month. Serum triglyceride levels increased 7.1% (8.0 mg/dl) during the study, but this was not significant and there were no differences between the groups (Table I).

Statistical analysis of the lipid data was performed with the baseline and 12-month values. Variations were noted in the trends of lipoprotein profiles that were obtained every 3 months. Cholesterol levels demonstrated a major decrease at 3 months, rose at 6 months, and then decreased until the end of the study. High-density lipoprotein cholesterol levels rose at 3 and 6 months and then remained unchanged. Subfraction 2 of high-density lipoprotein cholesterol levels rose until 9 months with no further change, whereas subfraction 3 decreased until 6 months and then did not change. Low-density lipoprotein cholesterol levels decreased at 3 months with a slight trend downward for the rest of the study. Very low–density lipoprotein cholesterol and triglyceride levels had the maximum increase at 6 months and then decreased slightly until the end of the study.

The bleeding data were evaluated in two ways. The first way was to divide the 52 weeks into four 13-week quarters and the second was to divide the 52 weeks into 13 4-week blocks. Any vaginal spotting or bleeding during a 24-hour day was considered an episode of bleeding. There were an average of 9 episodes of bleeding per patient in the first quarter compared with 4.5 in the second quarter ($p < 0.0005$). This diminished to 1.7 episodes in the third quarter ($p < 0.5$ comparing second and third quarters) and 1.3 in the fourth quarter, which was not a significant change from the third to the fourth quarter. Comparing the bleeding data with 4-week blocks, significant changes ($p < 0.05$) were noted in the second to third block, fourth to fifth block, and seventh to eighth block. The remainder of the changes were not significant. No differences were noted comparing the two treatment regimens.

Of the patients enrolled in the study, 35% had no bleeding during the 52 weeks. During the first 13 weeks, 43% did not bleed. This increased to 61% during weeks 14 to 26, 73% in weeks 27 to 39, and 82% in weeks 40 to 52. The distribution of the absence of bleeding was the same in both treatment groups.

Urinalysis, mammograms, liver function, creatinine, and fasting serum glucose test results demonstrated no significant changes during the study.

Endometrial biopsy specimens at the initial visit showed either atrophic or minimal tissue that was insufficient for diagnosis in the 92 patients. Twenty-one patients did not complete the study, leaving 71 patients, one of whom refused biopsy at study termination and one who underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy for an ovarian mass. Of the 69 endometrial biopsies performed at the conclusion of the study, 67 showed atrophy or had minimal tissue that was insufficient for diagnosis. Two patients demonstrated proliferative endometrium, both being in the group receiving 2.5 mg of medroxyprogesterone acetate.

Improvement was noted during the study in all the patients who had vasomotor symptoms at the time of the initial evaluation.

Twenty-one patients dropped out of the study at various intervals. Fourteen were in the group receiving 2.5 mg of medroxyprogesterone acetate and seven were in the group receiving 5 mg. Seven patients moved and were lost to follow-up. Two patients had unexplained rashes, one was too busy to keep her clinic appointments, one had multiple nonspecific somatic complaints, one had bloating and cramps, and one had unexplained abdominal pain at week 31 of the study. Eight patients discontinued the study because of vaginal bleeding. Six were in the 2.5 mg group and stopped at 4, 6, 12, 18, 18½, and 19 weeks of the study. Two patients were in the 5 mg group and stopped at 9 and 16 weeks of the study. There were no statistical differences between the two treatment groups in patients who dropped out because of bleeding.

Comment

The average American woman will live one third of her life after the onset of the climacteric, and it is becoming accepted that exogenous sex hormone therapy is appropriate for many of these patients. A 1986 bulletin from the Food and Drug Administration states that "short-acting estrogens are indicated in postmenopausal women with evidence of loss or deficiency of bone mass, to retard further bone loss, and estrogen deficiency–induced osteoporosis."[11]

There are certain well-accepted facts regarding estrogen therapy. Its use protects against osteoporosis,[12] unopposed use increases the risk of endometrial cancer,[13] the risk of cardiovascular disease is decreased with estrogen use,[14, 15] and vasomotor symptoms are adequately prevented by taking estrogen.[5] Also, the addition of a progestin for 10 to 14 days of each estrogen cycle reduces the risk of endometrial cancer to baseline or lower.[16]

The 0.625 mg dose of conjugated equine estrogen has been selected because it is adequate to obtain the beneficial effects of estrogen therapy in most postmenopausal women. The dose of 2.5 or 5.0 mg of medroxyprogesterone acetate was chosen with the rationale of protecting the endometrium while utilizing a dosage that will have minimal or no effect on serum lipoprotein levels.

Current areas of concern that we desire to address are the proper regimen of estrogen-progestin to protect the endometrium from neoplasia, minimize vaginal bleeding, treat vasomotor symptoms, and favorably affect the lipid profile. Several recent publications have suggested that a continuous combined low-dose regimen of estrogen-progestin eliminates the majority of vaginal bleeding and has either a beneficial or neutral effect on lipid profiles.[6, 17] This is in contrast to evidence that the use of 10 mg of medroxyprogesterone acetate for 10 days of each cycle has a negative effect on the high-density lipoprotein cholesterol level and its subfraction 2.[18]

It is important to appreciate that cardiovascular disease is a major cause of death in postmenopausal women.[4] Small changes in lipoprotein profiles may have major effects on rates of coronary heart disease. The Lipid Research Clinics Trial demonstrated that a 1% reduction in cholesterol level equaled a 2% reduction in coronary heart disease, and an 11% decrease in low-density lipoprotein cholesterol levels resulted in a 19% decrease in coronary heart disease.[19] A 1 mg/dl increase in high-density lipoprotein cholesterol levels may be associated with a 3% to 5% decrease in coronary heart disease.[20] The protection to the cardiovascular system by high-density lipoprotein cholesterol has been primarily attributed to its subfraction 2.[21] Ottosson et al.[18] demonstrated in a group of women treated with 2 mg of estradiol valerate a 9.2% increase in high-density lipoprotein cholesterol levels and a 16% increase in subfraction 2.[18] By the end of the third cycle, 10 mg of medroxyprogesterone acetate given for 10 days had basically eliminated these beneficial increases in serum lipoprotein levels.[18] The current study demonstrated a 2.8% or 6.8 mg/dl decrease in total cholesterol levels, a 4.5% or 2.5 mg/dl increase in high-density lipoprotein cholesterol levels, a 6.3% or 2.6 mg/dl increase in subfraction 2 of high-density lipoprotein cholesterol levels, a 7.6% or 12.3 mg/dl decrease in low-density lipoprotein cholesterol levels, a 5.2% or 1.2 mg/dl increase in very low–density lipoprotein cholesterol levels, and a 7.1% or 8.0 mg/dl increase in serum triglyceride levels. All of these changes are beneficial for protection from coronary heart disease and support the concept that low-dose continuous medroxyprogesterone acetate does not negate the beneficial effects of estrogen therapy on lipoprotein profiles.

Compliance is a serious problem with hormone-replacement therapy in the menopausal patient. Evi-

dence suggests that only 30% of patients are compliant with therapy, with fear of cancer being the major reason for discontinuing therapy.[22] Vaginal bleeding is a major symptom that distresses many patients receiving hormone-replacement therapy. Two recent studies demonstrated that only 50% of patients receiving continuous combined low-dose estrogen-progestin therapy had bleeding, with most episodes being spotting, and that it diminished with time.[6, 23] This is most likely the result of atrophic endometrium developing in the majority of patients receiving continuous combined therapy.[24]

Seventy-seven percent of the patients completed the 52-week study. Eliminating the patients who dropped out of the study for causes other than bleeding, the compliance rate increased to 90%, far above that expected for a sequential hormonal regimen.

The current data demonstrate a marked decrease in episodes of vaginal bleeding from an average of 9.1 episodes in the first 13-week block to an average of 1.7 episodes in the third 13-week block. Also, all patients had atrophic endometrium except for two taking 2.5 mg of medroxyprogesterone acetate who had proliferative changes. This regimen offers a substantial decrease in bleeding episodes and marked protection to the endometrium from development of a neoplastic process.

Debate exists as to the need for a baseline endometrial biopsy before starting hormone-replacement therapy. We do believe it is beneficial to obtain the endometrial biopsy specimen to rule out asymptomatic disease but appreciate that evidence exists that administration of progesterone to symptom-free postmenopausal women revealed those who did not have any vaginal bleeding to have had nonpathologic endometrial histologic findings.[25] It remains to the clinician to decide which method to use for baseline endometrial evaluation. Because most endometria remain atrophic with continuous combined low-dose estrogen-progestin regimens, it suggests that the clinician need only repeat the biopsy in those patients who have a marked change in vaginal bleeding while receiving the therapy.

The subtle differences noted between the two dosages of medroxyprogesterone acetate (2.5 and 5.0 mg) do not allow us to significantly distinguish one as being better than the other. Our suggestion is to start with the 2.5 mg dose along with a 0.625 mg dose of conjugated equine estrogen and, if spotting is heavy or persistent with normal endometrial histologic results, to increase to the 5 mg dose. This is an empiric suggestion and needs scientific substantiation.

It is our opinion that the use of a sequential regimen of estrogen-progestin does not increase the risk of breast cancer. The impact of a continuous low-dose regimen of estrogen-progestin on the incidence of breast cancer is unknown, but we believe that it is unlikely to be increased.

It is our belief that we have demonstrated the marked benefits of a continuous combined low-dose estrogen-progestin regimen for the menopausal patient. Menopausal symptoms are diminished, lipoprotein profiles are beneficially altered to protect the cardiovascular system, vaginal bleeding is diminished, and the endometrium is protected from neoplasia. As clinical evidence for the advantages of this approach accumulates, it is a possibility that this regimen will be the primary one for hormone-replacement therapy in the menopausal patient.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. ROBERT W. REBAR, Cincinnati, Ohio. No less an authority than the esteemed epidemiologist Dr. Elizabeth Barrett-Connor has stated that, "For the average North American woman, who will be postmenopausal for one third of her life, the benefits of estrogen seem strongly established."[1] However, both the risks and side effects of estrogen-replacement therapy in postmenopausal women have caused clinicians to investigate new and different ways of administering estrogens. Moreover, as the First International Consensus Conference on Progestogen Use in Postmenopausal Women concluded, "Basic science, clinical, and epidemiological studies have shown that progestogen treatment is efficacious and is indicated for opposing the effects of oestrogen on the endometrium."[2] Such considerations have led a number of investigators and pharmaceutical houses to suggest the use of continuous low-dose estrogen-progestin therapy for postmenopausal women.

This article summarizes a pharmaceutical company–sponsored study aimed at documenting the efficacy of combined estrogen-progestin therapy. It is presumed that such therapy will reduce the incidence of uterine bleeding and the risk of endometrial hyperplasia while not adversely affecting the beneficial effects of estrogen on the ratio of high-density to low-density lipoprotein cholesterol. Moreover, no such study has attempted to evaluate what should be the optimal ratio of estrogen to progestin in such therapy. The selection of the dosages of each steroid is empiric, being based on data collected from patients receiving sequential therapy.

Unfortunately, the design of the present study, as well as of most such clinical trials, does not directly prove or disprove such assumptions. In the present study no control patients were included who took no estrogen (placebo), estrogen alone, or sequential estrogen and progestin for the entire year. Thus it is impossible to determine if combined estrogen-progestin therapy is more efficacious than any of these other modes of therapy. It should be noted that the same consensus conference on progestogen use concluded that it is ethical to include a study group of women who have not undergone hysterectomy who are receiving unopposed estrogen in carefully monitored clinical trials.[2] However, no consensus was reached on the inclusion of a placebo group receiving no hormonal therapy.

Thus your conclusion that your data ". . . support the concept that low-dose continuous medroxyprogesterone acetate does not negate the beneficial effects of estrogen therapy on lipoprotein profiles" is inappropriate. True, you did demonstrate an increase in high-density lipoprotein cholesterol and a decrease in low-density lipoprotein cholesterol levels. However, this study does not prove that the beneficial effects are not less than those of estrogen alone or estrogen administered sequentially with a progestin. Given than, as you noted, even "small changes in lipoprotein profiles may have major effects on rates of coronary heart disease,"[8] the omission of these control subjects is of major significance.

You state that you could not distinguish any significant differences between the 2.5 and 5.0 mg doses of medroxyprogesterone. In view of evidence that the progestogenic effects on lipoprotein cholesterol levels are dose dependent,[3] it would seem prudent, as you suggest, to use the lowest dose of progestin that prevents endometrial hyperplasia.

In addition, it is possible that any reduction in the incidence of coronary heart disease in women taking estrogen is in part the result of some other or as yet unidentified property of exogenous estrogens. For example, estrogens appear to cause vasodilatation by stimulating prostacyclin production.[4,5] Progestins appear to have the opposite effect, abolishing this stimulation of prostacyclin production. It is also possible that this property is antagonized by progestin. Only longer-term studies comparing sequential and continuous estrogen-progestin therapies will determine if there is any difference between the therapies.

Also not considered in the current study are the effects of progestins quite apart from antagonizing the effects of estrogens. Progestins have significant effects on liver enzymes. The long-term consequences of any progestin-induced changes remain to be identified.

As presented, the bleeding data are unclear. You tell us that any vaginal spotting was considered 1 day of bleeding. You than go on to discuss the number of "episodes of bleeding." It is not clear if an "episode" is equivalent to 1 day or to an interval of continuous bleeding for 1 or more days. Also of note is your observation that the bleeding was not significantly diminished in the fourth quarter compared with the third

quarter of this year-long study. Moreover, no data are provided as to how many of the women did and how many did not continue to bleed during the study. The patterns of bleeding observed are not discussed as well.

In this regard, the failure of 21 patients to continue estrogen-progestin therapy during the course of this study is particularly disconcerting. Apparently only 8 of the 92 patients discontinued this study because of vaginal bleeding. However, there can be no doubt that these women were particularly motivated: they had elected to participate in a research study and were probably compensated reasonably well for completing the study successfully. What percentage of treated women who are not part of a study and who are receiving continuous estrogen-progestin therapy will discontinue the medications if there is any irregular and unexpected bleeding?

Although the investigators tell us that all the patients who had vasomotor symptoms at the time of initial evaluation were improved with therapy, no data are presented. Because it is possible to quantitate hot flushes objectively and subjectively, such data should be available. Similarly, the effect of the estrogen-progestin therapy on calcium excretion and bone density over time are also needed to evaluate this therapy completely. In addition, the depressive effects of progestogens are well known. The investigators should provide us with data that daily combined therapy did not have a negative impact on the psychologic states of the women.

Strangely absent from the discussion is any consideration of the effects of combined estrogen-progestin therapy on the incidence of breast cancer. Clearly the present study cannot answer this important question. Opinions are divided on this issue. The observation that maximal mitotic activity in breast tissue occurs on about day 25 of the normal menstrual cycle at the time of maximal progesterone secretion by the corpus luteum suggests differences in cellular activity compared to the endometrium.[6] Maximal mitotic activity in the endometrium occurs in the follicular phase of the cycle, with glandular tissue being shed monthly. Henderson et al.[7] have suggested that progestins cannot be presumed to have an antiestrogen anticancer effect on the breast, and others have reached this same conclusion more recently.[8] Longer and larger trials will be required to determine if exogenous estrogen alters the risk of breast cancer in postmenopausal women and to determine how the addition of a progestin modifies the response to estrogen.

In summary, your study presents important data about the possible role of continuous combined low-dose estrogen-progestin therapy for postmenopausal women. However, the study has significant weaknesses, as must be true of any study involving a small number of patients followed up for only 1 year. Data from larger and longer studies are required before definitive conclusions can be drawn about the relative efficacy of combined therapy. Until such data are available, it is my opinion that it is unwise to recommend anything except sequential therapy to postmenopausal women who have a uterus. Moreover, because of the potentially harmful effects of progestins, it seems prudent to administer estrogens alone to postmenopausal women who have undergone hysterectomy. To some, these may be regarded as controversial recommendations. I would suggest, however, that these are prudent and cautious suggestions and would note in closing the comments of the First Consensus Conference on Progestogen Use in Postmenopausal Women: "There are insufficient long-term histological and epidemiological data to advocate the routine use of daily doses of both progestogen and oestrogen (continuous-combined therapy). The long-term metabolic consequences of daily progestogen addition need to be determined."[2] For the sake of impartiality, I must note that this conference also went on to conclude, "However, continuous-combined therapy may be an option."[2]

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DR. RONALD T. BURKMAN, Detroit, Michigan. Devising an appropriate regimen for hormone replacement therapy during menopause is a subject of considerable topical interest, given the estimated 40 million women in the United States who are potential candidates for this therapy. However, for a variety of reasons it has been estimated that only 10% of the potential candidates for hormone replacement actually take the medication.[1] On the benefit side of the ledger is relief of vasomotor symptoms, reduction of bone mineral loss, and probable reduction in coronary heart disease, whereas on the risk side one includes neoplasia (endometrial and possibly breast) and perhaps gallbladder disease. You have evaluated two continuous combination approaches and have examined resultant endometrial histologic findings during a 1-year trial period.

In regard to the lipid-lipoprotein changes, both regimens appeared to demonstrate favorable effects, with mean changes from baseline varying between 1% and 10%. However, when one examines the standard deviations, there seems to be considerable variability. Be-

cause data were collected at two institutions, it would be important for you to provide us with information as to what was done to ensure that the results between the two institutions were comparable. Although the two treatment groups did not show statistically significant differences relative to lipids and lipoproteins, there were trends, albeit inconsistent ones, that suggest that the regimens might differ in important ways. For example, the group taking 2.5 mg of medroxyprogesterone acetate showed a 7.4% increase from baseline for high-density lipoprotein cholesterol levels, whereas the group taking 5 mg showed only a 2.2% increase, a difference that may be of some clinical significance. Clearly the final sample sizes of 31 and 40 subjects are too small to evaluate this issue adequately. As an aside, it should be noted that all investigators use lipid-lipoprotein changes as a proxy for coronary heart disease because the measurement of outcome variables such as myocardial infarction would require prohibitively large sample sizes for clinical trials, as well as create other design problems. Although the relationship of lipid-lipoprotein changes to incidence of coronary heart disease has been well established in several studies, it is important to recognize that recent animal studies suggest that sex steroids may also act outside the lipid-lipoprotein system to such an extent that lipoprotein changes could become less predictive of later risk of coronary heart disease.[2]

In regard to vaginal bleeding, it appears that the frequency of bleeding declined over time; significant differences between the treatment groups were not presented. However, the study dropout rates suggest that the lowest-dose progestin regimen was less acceptable because 13% of women in this group compared with 4% in the higher-dose group discontinued the study because of bleeding.

The endometrial histologic data also suggest that the lower-dose progestin regimen may be less effective than the higher-dose regimen in maintaining atrophic conditions. Of the women who completed the study, two or 6.5% of the women in the group taking 2.5 mg of medroxyprogesterone acetate showed conversion from an atrophic to a proliferative endometrium. Whether this dose would place women at undue risk for endometrial cancer is unknown. An obvious question is, how does one monitor patients on a continuous combination regimen particularly if there is inconsistency in the bleeding patterns? Although Padwick et al.[3] have suggested a useful approach for women receiving sequential hormone-replacement therapy, it is not an approach that can be used with continuous combination therapy. Scientifically, this concern may become less of an issue if the cardiovascular-protective actions of estrogen replacement continue to be borne out. As suggested in the "risk model" of Ross et al.,[4] far more women would be saved from cardiovascular deaths than would be lost from endometrial cancer, even if we elected not to prescribe a progestin with the estrogen. However, whether consumers would accept fewer heart attacks for more cancer is unclear. In any event, the task that faces us is to make these medications not only efficacious and safe but also far more acceptable, particularly from the standpoint of side effects. More clinical trials are needed to allow us to define approaches better that fit our patients' needs.

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Dr. Eduard Eichner, Cleveland, Ohio. Having been with research for years, the sequential treatment, as far as I am concerned, is out in therapy because it produces bleeding in almost 100% of women; therefore they drop out of the study. I am not talking about the efficacy in "saving things" but in getting patients to do a study.

Dr. Russell Malinak, Houston, Texas. Did you correlate the time of onset of the menopause with abnormal bleeding on your regimens? It has been a clinical observation that women in the early postmenopausal period will tend to have more abnormal bleeding than have women in the late postmenopausal period.

Dr. Weinstein (Closing). To answer some of the questions that were addressed, first the concept of menopause that I accept is that it is a hormone-deficient state. If one accepts that and makes an analogy to hypothyroidism, I do not think you can have a control group in a current study. I personally would not do a study that has a control group of patients without any hormonal therapy.

The other thing would be to use estrogen-only therapy in the patient with an intact uterus. I think you can do that, but I do not know who is going to accept the risk if an atypical endometrial hyperplasia develops, regarding the cost of the curettage and the potential for surgery and related hysterectomy. I think it is a difficult issue.

There are superb data regarding unopposed use of estrogen as related to the development of endometrial carcinoma. I personally have difficulty with it, although I admit that unopposed estrogen in the majority of patients is a very good therapy; unfortunately, in the society we live in I am not sure we can do that any more.

If one looks at our lipid data, the reasons that we did not have control groups are as I stated. However, if you compare our lipid data with those of the Lipid Clinic Research Study that was published in *The New England Journal of Medicine* of patients treated with estrogen only with measured lipid profiles, our lipid data are similar. There is no major difference. If one will accept this historic control, I believe it shows that

lipid data of the low-dose continuous regimen are not affected by the medroxyprogesterone acetate.

A major reason for a study like this is to improve compliance. Use of sequential hormonal therapy is very nice. You give it to the patients, they go home, and you do not see them again. Also, they do not get repeat prescriptions. There are some excellent data from the Boston group that show that the average compliance for sequential hormonal therapy is 30% to 40%. If we truly have a hormone-deficient state and we really want to help the health care of aging women, I think we have to have a regimen with a better compliance record.

Dr. Burkman commented about the samples. All the samples were run by one central research laboratory. They were collected at the two institutions, but they were all run in one place, so the variation should be the same. The 2.5 mg regimen did have a better lipoprotein profile with increased high-density lipoprotein levels, and that is why we suggest that one start with a 2.5 mg regimen. The patients who have continuous nuisance spotting that goes on for more than 20 weeks are the patients we think will benefit from the 5 mg dosage. In general in our clinic population we start at the lower dosage.

How do you monitor the patients? Well, the question is always asked, do you do yearly endometrial biopsies? If you have a baseline endometrial biopsy result, you know where you are going, and you know from where you started. If you do not have an endometrial biopsy as a baseline, and the patient has bleeding, I do not think you have any idea where you are because you really do not know where you started.

So we do the baseline biopsy study, and then we repeat it if the patient has any unusual change in bleeding patterns. In the last 3 years in the two combined studies we have done, it has been necessary to repeat one endometrial biopsy that demonstrated atrophic changes. At this time we do not advocate yearly or repeat endometrial biopsies.

The question by Dr. Malinak regarding the time of onset of menopause, our patients averaged 55 years of age. They were at least 1 year menopausal. We had no patient in the study over 60 years and none under 46 or 47 years, as I recall. So our patients tended to be on the young side of menopause, and his point is well taken that younger women, both menopausal and perimenopausal, tend to have the most bleeding problems.

Ultrasonography and external cephalic version at term

William L. Donald, MD, and John J. Barton, MD

Chicago, Illinois

Sixty-five patients with nonvertex presentations at term were evaluated by ultrasonography to determine which factors were associated with a successful external cephalic version. Amniotic fluid volume, placental localization, type of breech, position of the fetal spine, and whether the breech had descended were determined and analyzed by χ^2 analysis. Only a frank breech and an anteriorly located fetal spine were associated with a successful version. Four episodes of fetal bradycardia occurred, none requiring operative intervention. There were no episodes of maternal bleeding or dislodgement of the placenta. Fifty-eight percent of all breech presentations were converted and 62% were delivered vaginally. We conclude that ultrasonography is useful in the evaluation of patients with a nonvertex presentation at term and can be used to predict which patients are likely to undergo a successful external cephalic version. (Am J Obstet Gynecol 1990;162:1542-7.)

Key words: Ultrasonography, external version

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6/6/20136

The cesarean section rate has risen progressively from 4.0% in 1970 to 24.6% in 1986.[1] In 1970, 14.0% of infants in breech positions were managed by cesarean delivery; in 1986 that number was up to 86%, and in some centers 100% of breech presentations are managed by cesarean delivery.[1] Fig. 1 shows the recent trend of breech deliveries at Illinois Masonic Medical Center.

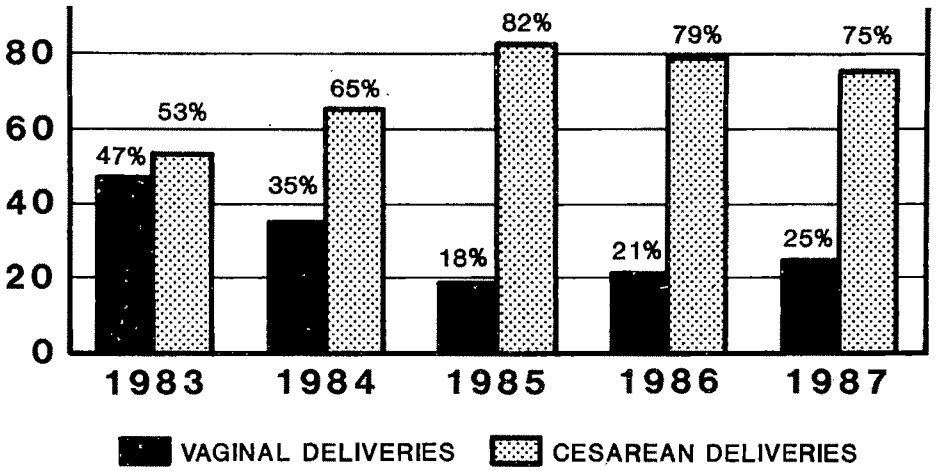


Fig. 1. Management of breech presentation at Illinois Masonic Medical Center.

External cephalic version has been shown to be successful in managing the nonvertex presentation at term.[2-4] Ultrasonography has assumed an important role in the assessment of these patients. The purpose of this study was to assess which factors detected on ultrasonographic evaluation of nonvertex presentations at term are associated with a successful external cephalic version under tocolysis.

Patients and methods

From July 1986 through October 1988 all patients with a nonvertex presentation at term referred from private obstetricians, the nurse midwifery service, and the obstetric clinic of Illinois Masonic Medical Center were included in the study. Exclusion criteria are listed in Table I. No patients referred were in labor. All patients who met inclusion criteria were asked to participate. All patients underwent nonstress testing before the start of the procedure, an intravenous line was begun on all patients, and all patients signed an informed consent for external cephalic version and emergency cesarean delivery. An ultrasonographic evaluation was then performed on all patients. The parameters evaluated were amniotic fluid volume, fetal lie, and presentation. If breech, the type of breech was determined by assessment of the relationship of the lower limbs to the fetal abdomen. The descent of the breech into the pelvis was assessed and in several cases confirmed by vaginal examination. The position of the fetal back was determined: anterior or posterior. The location of the placenta was determined: predominantly anterior or posterior. Rather than using amniotic fluid index as described by other investigators, our criterion for decreased amniotic fluid was defined as a vertical pocket of fluid less than 2 cm in depth. All data on each patient were entered onto a fact sheet and later analyzed. A

Table I. Exclusion criteria

Placenta previa
Antepartum hemorrhage
Previous uterine scar
Multiple pregnancy
Uncontrolled hypertension
Rupture of membranes
Less than 37 completed weeks
Evidence of placental insufficiency or fetal distress
Morbid maternal obesity

prophylactic tocolytic was initiated in all cases. There are many studies in the literature that do not use a tocolytic as part of the version attempt. We thought that a tocolytic was needed and is our preference in performing versions. The tocolytic used was ritodrine (Du Pont Pharmaceuticals, Wilmington, Del.). It was begun 30 minutes before the version attempt. The external cephalic version method as described by Ranney[5] was used. All versions were done by the same physicians. Patients were monitored for 1 hour after each version, regardless of whether the attempt was successful. A maximum of two attempts at one sitting was made on each patient.

Data were analyzed by the χ^2 method with Yates' correction and the Fisher exact test.

Results

Sixty-five patients were enrolled in the study. Thirty-eight (58%) of the patients underwent a successful version. Forty-one (63%) of the patients studied were delivered vaginally, including those with successful conversions, four persistent breech presentations, and three spontaneous cephalic versions. The spontaneous cephalic conversion rate of 4.6% is similar to results that have been reported by other investigators.[6, 7] Of

Table II. Illinois Masonic Medical Center criteria for vaginal delivery of breech presentation

Frank or complete breech
Level II ultrasonography for fetal anomalies
One mediolateral film for flexion
Absence of uterine disease (e.g., cesarean section scar or cervical fibroids
Progressive and appropriate descent of fetal buttocks during active phase of labor
Obstetrical service team (including nursing staff) alerted and prepared to do Dührssen's incision
X-ray pelvimetry in primigravidas at obstetrician's discretion, but not mandatory

Table III. External cephalic version results

	Successful		*Vaginal delivery*	
	n	%	*n*	%
Frank breech	20/28	71	22/28	79
Complete breech	8/15	53	8/15	53
Incomplete breech	3/10	30	3/10	30
Total	31/53	59	33/53	63

the 27 unsuccessful attempts, 20 of the patients underwent cesarean delivery. There were four vaginal deliveries of frank breech presentations; we used criteria developed at our institution for breech delivery. These criteria are listed in Table II. Table III shows the external cephalic version results, and Table IV shows the results of statistical analysis of the data. The greatest success was obtained with a frank breech presentation and when the fetal spine was in an anterior position. This is somewhat contrary to the current theory that the amniotic fluid volume is the most important criterion for a successful version. Obviously, in cases in which oligohydramnios, as defined by our criteria, was present, a vigorous attempt to convert the fetus was not used. Further fetal evaluation was done to determine any causative pathologic factors for the oligohydramnios. There were four episodes of fetal bradycardia in the 65 patients. There were no fetal or maternal deaths in the study group. Twelve patients in the study presented with a transverse lie. These patients were excluded from the totals in Table III. They constitute a separate study group.

Comment

External cephalic version has been shown to be effective in the management of the breech presentation at term and in reducing the cesarean section rate in breech presentations at term.[7-9] Ultrasonography has assumed an important role in the management of these patients. We used ultrasonography to evaluate all patients undergoing an external cephalic version at term. The objective was to determine which factors were associated with a successful version. We found only two: the type of breech and the position of the fetal spine. Unlike Ranney,[5] who found decreased amniotic fluid volume to be responsible for 14.8% of his failed versions, we did not find this association. We did not aggressively attempt version in these cases and submitted these patients to further testing to determine if there were any associated pathologic processes causing the oligohydramnios. Neely,[10] who used an anesthetic during his versions, found 17.8% of his failures to be the result of a decreased amniotic fluid volume. Decreased amniotic fluid volume has been considered to be a relative contraindication to an external cephalic version.

Fianu and Vaclaviahova[11] had a 96% success rate when the placenta was implanted on the anterior or posterior uterine wall and only a 44.4% success rate when the placenta was cornual or fundal. Placental location, with the obvious exception of placenta previa, was not found to be of significance in our study. Initially, cornual and fundal placental locations were evaluated, but then we assigned them to either anterior or posterior groupings depending on where the major

Table IV. Results of statistical analysis

Parameter	χ^{2}*	*p Value*
Amniotic fluid volume	1.548	NS
Placental location	3.642	NS
Station in pelvis	0.692	NS
Breech type (frank vs others)	5.300	<0.05
Fetal back position	9.061	<0.01
Breech vs transverse lie	0.112	NS
Parity	0.015	NS

*With Yates' correction.

Table V. Morbidity and mortality results for the breech deliveries at Illinois Masonic Medical Center

Year	*<2500 gm (n)*	*>2500 gm (n)*
Vaginal route (n = 101)		
1983	5: 3 stillbirths, 2 perinatal deaths	0
1984	0	0
1985	2: 2 perinatal deaths	0
1986	8: 6 perinatal deaths, 2 clavicle fractures	0
1987	4: 4 perinatal deaths	0
Total	19	
Cesarean route (n = 253)		
1983	0	0
1984	1: 1 perinatal death	0
1985	0	0
1986	5: 5 perinatal deaths	0
1987	4: 4 perinatal deaths	0
Total	10	0

part of the placenta was located. An anterior placenta has been considered to be a relative contraindication to an external cephalic version by some authors.[3] Our data do not support either increased or diminished success.

Extension of the fetal legs and, as such, the type of breech presentation have been believed not to play a role if tocolysis is used.[12] We found in our study that a nonfrank breech was associated with a relative failure rate of the external cephalic version. Even under tocolysis, with an incomplete breech the fetal leg might serve as a splint, decreasing the ability to turn the fetus.

The posterior position of the fetal spine was associated with an increased rate of failure of external cephalic version in our study group. With the fetal back located posteriorly, only the soft parts of the fetus are palpable. They are more difficult to use as points of leverage in turning the fetus. The posterior position of the spine may also make the umbilical cord more vulnerable to compression during the version attempt. The four episodes of bradycardia in our study were associated with the back in a posterior position and were probably caused in this manner.

When the fetus in the breech position has descended into the pelvis, the success rate of the external cephalic version has been found to be decreased by some investigators. Strictly speaking, this is not an ultrasonographic factor; however, by placing the linear transducer at the level of the maternal symphysis pubis and repeatedly angling up and down, one is able to assess whether the presenting part has entered the pelvis or still lies above the pelvic brim. In our study we did not find this to be a factor. However, all of our patients were placed in a lateral tilt and Trendelenburg position before the start of the external cephalic version to prevent possible maternal supine hypotension. Such preparation may account for the reason that this was not found to be a factor in our study.

Without external cephalic version, about 3% to 4% of all term deliveries would be in breech presentation.[13, 14] Vaginal delivery of the unselected breech infant at term is associated with an increase in perinatal mortality rates. Compared with the vertex presentation at term, there is a threefold increase in the mortality rate and a twelvefold increase in the morbidity rate in unselected cases.[15] Our criteria for vaginal delivery of an infant in the breech position are listed in Table II, and our results for the years 1983 through 1987 are shown in Table V. The trend in contemporary obstetric practice has clearly been toward cesarean delivery for the breech presentation. External cephalic version provides an attractive alternative to this longstanding and controversial obstetric dilemma. In this study we found a frank breech presentation and the fetal back in an anterior position to be the factors on ultrasonographic evaluation associated with a successful external cephalic version. We did not find that amniotic fluid volume, placental location, or station of the presenting part to be of significance in the success of the version. We conclude that ultrasonography with tocolysis is useful in the evaluation of all patients with a nonvertex presentation at term undergoing an external cephalic version. All patients should be offered this procedure, and in the hands of an experienced obstetrician it may reduce the morbidity and mortality rates associated with vaginal breech delivery, including cesarean delivery of the infant breech at term.[16]

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. SAM T. SCALING, Casper, Wyoming. This is an interesting study attempting to delineate further the

factors associated with successful external cephalic version in patients at term. The overall success rates are comparable to those of other studies of external cephalic version at term.

Although the factors in this study associated with successful version at term, that is, frank breech presentation and anteriorly located fetal spine, may help predict which patients will have a successful version, the clinical absence of these factors should not deter a clinician from attempting external cephalic version in most or all patients with nonvertex presentations who otherwise have no contraindications to the procedure.

Second, it would be good to know if any of the factors studied would be associated with increased morbidity or complications such as bradycardia, isoimmunization, or even significant patient discomfort. Indeed this was determined with one factor, the posterior position of the fetal spine and the apparent relationship to the occurrence of bradycardia. Because the essence of a successful version also includes safety to both the mother and fetus, it becomes imperative that factors that increase morbidity or mortality rates be known.

The cases of transverse lie are included in the statistical analysis of the data, but the successful factors found (frank breech and position of the fetal spine) do not seem to apply in analyzing these cases. By removing the cases of transverse lie from your Table II, the overall success rates for version in breech presentations remain the same. In analyzing the data and factors that apply to version in breech presentation, it seems more prudent to consider transverse lie as an entirely separate study and analyze accordingly.

I have two questions relating to antepartum hemorrhage as an exclusion factor in your study. First, how did you define antepartum hemorrhage in your study? Second, since up to 20% of obstetric patients will have antepartum hemorrhage and only about 50% of those who bleed have a resultant pregnancy loss, by ruling out placenta previa with ultrasonography should not some of this subset of patients be afforded the opportunity for external cephalic version?

Dr. Peter K. Thompson, Houston, Texas. This study helps us move, ever so slowly, toward better understanding and hopefully acceptance of external cephalic version. An objective was to find if ultrasonography could predict the probability of success in external cephalic version. It is interesting to know that of the eight factors studied only two had any association. Your results suggest that we should be more optimistic about external cephalic version if the breech position is frank and the fetal spine is anterior. Conversely, should the lack of these two factors preclude an attempt at external cephalic version?

A similar article by Fergerson et al.[1] in 1987 studied maternal and fetal factors before external cephalic version in 172 patients. In their study, factors associated with success were (1) noncornual placental location, (2) normal or increased amniotic fluid, (3) nonfrank presentation, and (4) fetal spine in the lateral position. In 1988 Fortunato et al.[2] reported on 67 patients and they found only two significant negative factors: descent of the breech presentation and fetal spine in the posterior position. Consequently, you, Fergerson et al., and Fortunato et al. agree only that the position of the fetal spine is a significant factor in predicting success. It should be mentioned that even when the position of the fetal spine was unfavorable (posterior), the success rate with external cephalic version was at least 48% in the study by Fergerson et al. but only 13% in the study by Fortunato et al.

I have often heard the comment from detractors of external cephalic version that successful versions represent those fetuses that would probably turn spontaneously if left alone. In this study the spontaneous cephalic conversion rate was 4.6%. We know that in studies with control subjects[3, 4] the rate of spontaneous version after 36 to 37 weeks is 14% to 20%. The rate can be as high as 30% in multiparous patients.[5] In the majority of studies on external cephalic version, when attempted beyond 37 weeks the success rate is at least 45% and more often 60% to 70%. Certainly these facts do not support the attitude of leaving the breech alone in hopes of a spontaneous conversion.

I have two questions: first, why did you use only anterior and posterior localization of the placenta and delete the cornual and fundal category? As mentioned earlier, other investigators have been able to show that cornual implantation decreases the success rate. Second, what is your opinion about the need for ultrasonography in external cephalic version other than to confirm the presentation if there is doubt? I believe the information obtained by a full ultrasonographic examination seems to be of minimal prognostic value and its cost would not justify its routine use. Perhaps the place for detailed ultrasonographic findings may be to explain why a procedure failed or convince the physician not to try again.

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Dr. Washington Hill, Omaha, Nebraska. In your protocol you mentioned obtaining a mediolateral film for evaluation, I assume, of hyperextension of the head. You went over that rather quickly. Could you give us some further information on that because that is something that many of us do not do.

Did you consider using an alternative tocolytic? Since you mention that some patients do not like the side effects of ritodrine, perhaps some other tocolytic such as magnesium sulfate might be helpful.

Did you consider having a Kleihauer-Betke stain done on patients who had an anterior placenta to see whether they had any fetal-maternal hemorrhage? I was somewhat surprised that you did not find the station of the breech to reduce your success rate, because many of us have found that the engaged breech is somewhat hard to turn.

Dr. Kenneth Moise, Houston, Texas. Did you use a two-operator technique or a single-operator technique?

Dr. Robert W. Rebar, Cincinnati, Ohio. What was the outcome of the infants who were treated with external version compared with those not so treated? Second, what was the difference with regard to the morbidity of the mothers in each group? Third, what was the difference with regard to costs incurred in each group? I would think that the answers to these questions would be interesting at least from the perspective of health care.

Dr. Daniel A. Rightmire, Springfield, Illinois. Were there recurring factors after version that prevented vaginal delivery? For example, cord presentation or compound presentation may follow a "successful" version and still result in cesarean delivery.

Dr Barton (Closing). The subject that Dr. Donald addressed is really just one thread in the whole cloth of the management of the breech presentation. Obviously, the attempts at external cephalic version are done to avoid facing the dilemma of whether to deliver the breech vaginally or abdominally. I present this statement to you: "In current obstetrical practice, vaginal delivery of a breech presentation is tantamount to malpractice." You will find this statement in the trial transcripts of an expert witness appearing in the Circuit Court of Cook County, Illinois, where the defendant had a bad outcome in a vaginal delivery of a fetus in breech presentation. I asked 12 of my colleagues if they had ever heard this statement made by one of their colleagues. Six different names were mentioned as physicians adhering to that standard.

At Illinois Masonic Medical Center we reviewed our statistics on the management of breech presentations and the perinatal outcomes. The questions we addressed were the following: Are we still managing breech presentations with vaginal delivery and, if managed vaginally, is this justified by outcome criteria; are we teaching our current generation of obstetricians the art and technique of vaginal breech delivery, or will we become one-operation technicians, performing only cesarean sections?

From 1983 through 1987 we had 10,476 consecutive deliveries. There were 344 breech presentations, for a rate of 3.28%. This is consistent with what we find in the textbooks for the incidence of breech deliveries. From 1983 onward, we caught on to the concept of cesarean delivery for the breech presentation, and the percent of vaginal deliveries reached a trough in 1985. Then we began to realize that our past professors such as Dr. Mengert and others were correct when they pointed out that the selected vaginal breech delivery with proper management skills was the tool in the trade and skills of obstetricians. As a result, the number of vaginal breech deliveries has begun once again to increase at some centers around the country, including ours.

In analyzing the perinatal outcome, one will find that in the unselected, unmanaged breech delivery that fell outside our criteria there was certainly poor perinatal outcome. However, in cases in which our criteria were met and the infant was 2500 gm or more the perinatal morbidity and mortality rate was 0%. Thus I believe that our data answer the questions that we posed, and, yes, obstetricians are still being taught the art of breech deliveries in Chicago.

In answer to some of the questions from the floor, only patients with antepartum hemorrhage in the third trimester were excluded from the study. We agree that the transverse lie probably constitutes a separate group of patients, and that group should be analyzed separately. However, it should be emphasized that in this group we were able to convert 57% of these patients to a cephalic presentation and achieve vaginal delivery in 67%. This group of patients should definitely be considered for external cephalic version and not routinely scheduled for cesarean delivery. Did we attempt an external cephalic version if all of our criteria were not met? Yes, we did in some cases; however, we expected, and did get, a higher failure rate in those patients. In answer to Dr. Washington Hill's question concerning the use of an alternative tocolytic, we felt comfortable with our methods and agents. In response to the question of whether we used the single- or double-operator technique, we used the single-operator technique, all performed by the same perinatologist: Dr. Donald. To answer Dr. Rebar, I think that perhaps the answers to fiscal economy are obvious. We are now delivering 25% of our breech presentations vaginally. All meet our criteria and, in my view, the most controlling factor for a favorable outcome was the steady and expected descent of the breech during the active phase of labor.

Cordocentesis for rapid karyotyping

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Pure fetal blood was obained by cordocentesis in 101 fetuses of 96 patients at 15 to 38 weeks' gestation. Rapid karyotype was obtained within 2 to 4 days by fetal lymphocyte culture. Chromosomal abnormality was detected in 12 (11.9%) fetuses. Abnormal karyotype was found in 5 of 44 fetuses with structural malformations, 3 of 13 fetuses with intrauterine growth retardation or oligohydramnios, 1 of 3 fetuses with nonimmune hydrops fetalis, 2 (one monozygotic set) of 10 discordant twins, 1 of 12 isoimmunized gestations, none of 8 cases with advanced gestational-maternal age, and none of 6 immune thrombocytopenia cases. This suggests that rapid karyotype should be obtained in all cases of fetal strutural malformations, intrauterine growth retardation, and nonimmune fetal hydrops, and may be obtained incidentally in isoimmunized pregnancies and discordant twins to assist in clinical management. (AM J OBSTET GYNECOL 1990;162:1548-53.)

Key words: Cordocentesis, rapid karyotype

Since Daffos et al.[1] first described their percutaneous umbilical blood sampling procedure for fetal blood sampling in utero, several reports[2-5] have appeared in the literature that describe its use for various indications. One important indication for percutaneous umbilical blood sampling, or cordocentesis, is rapid determination of fetal karyotype. Williamson et al.[6] reported on abnormal pregnancy sonogram as a selective indication to obtain fetal karyotype. In their report, amniocentesis and cordocentesis were used to obtain fetal karyotype.

Nicolaides et al.[7] reported on pregnancies with fetal anomalies detected by sonogram for which fetal blood samples were obtained with fetoscopy for the purpose of rapid karyotyping. Daffos et al.[8] performed cordocentesis in 39 of 562 cases for rapid karyotyping, Weiner[3] reported 33 cordocentesis procedures for rapid karyotyping, 24% of which had an abnormal karyotype. We hereby report our experience with 96 patients who underwent cordocentesis and had rapid determination of fetal karyotype.

Patients and methods

Patients who were referred to Vanderbilt University Medical Center between October 1986 and March 1989 and subsequently underwent cordocentesis are included in this report. Cordocentesis was performed under a program approved by the Committee for the Protection of Human Subjects, and all patients signed forms of informed consent for the procedure. Detailed high-resolution sonographic examination (SAL77A, Toshiba, Tustin, Calif.) was performed in all cases to confirm the diagnosis, assess the extent and severity of existing fetal anomalies, and exclude or identify other possible associated malformations. All patients underwent appropriate genetic counseling.

Fetal blood sampling was performed under local anesthesia with a 20 gauge 9 or 12 cm needle (Becton-Dickinson, Rutherford, N.J.) under full aseptic precautions and sonographic guidance by the method described by Daffos et al.[1] Sedation was occasionally induced for specific clinical indications, such as maternal anxiety or discomfort after initiation of the procedure. Tocolytic agents were not administered unless the patient was undergoing tocolytic therapy for preterm labor, or if localized uterine contraction occurred in response to needle insertion. The site of needle insertion depended on cord insertion and placental location. Fetal injection of pancuronium bromide (Pavulon, Organon Inc.) was rarely used, except in cases with posteriorly implanted placentas in which excessive fetal movement interfered with cord puncture. Fetal origin of the blood sample was determined by saline solution flush at the time of procedure, and purity was confirmed by the Kleihauer-Betke test.

Results

Mean maternal age of the study population was 27.1 years. Mean gestational age of the study population was 26.9 weeks, with a range of 15 to 38 weeks. The clinical indications for cordocentesis and the number of abnormal karyotypes found in each group are listed in

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Table I. Indications and results of rapid karyotyping

Clinical indications	*Total No. of fetuses*	*No. of abnormal karyotypes*
Fetal structural malformations	44	5
IUGR or oligohydramnios	13*	3*
Nonimmune hydrops fetalis	3	1
Advanced gestational—maternal age	8	0
Discordant twins	10	2
Isoimmunization	12	1
Immune thrombocytopenic purpura	6	0
Other	5	0
TOTAL	101	12

*One fetus with IUGR also had obstructive uropathy.

Table II. Findings in cases of renal or urinary tract abnormalities

No.	*Findings*	*Gestational age (wk)*	*Karyotype*
1	Obstructive uropathy	18	Normal
2	Obstructive uropathy	20	Normal
3	Obstructive uropathy	22	Normal
4	Obstructive uropathy	16	Normal
5	Echogenic multicystic kidneys	27	Normal
6	Bilateral hydronephrosis	30	Normal
7	Renal agenesis	35	46,XY(4p−)

Table III. Findings in abdominal-gastrointestinal abnormalities

No.	*Clinical findings*	*Gestational age (wk)*	*Karyotype*
1	Omphalocele	29	47,XX+18
2	Omphalocele	20	Normal
3	Ompahlocele	38	Normal
4	Omphalocele	27	46,XY−13+der(13) t(13q18p)
5	Gastroschisis	30	Normal
6	Small-bowel obstruction	25	Normal
7	Duodenal atresia	24	Normal

Table IV. Findings in umbilical cord abnormalities

No.	*Clinical findings*	*Gestational age (wk)*	*Karyotype*
1	Single umbilical artery	33	47,XY+13
2	Single umbilical artery Umbilical cord cyst Intraabdominal cyst	24	Normal
3	Single umbilical artery	32	Normal
4	Single umbilical artery Renal anomaly Clubbed foot and hand	32	47,XY+13

Table I. The major indications for rapid karyotyping were fetal anomalies and intrauterine growth retardation (IUGR) or oligohydramnios. Incidental rapid karyotyping was done in all cases of isoimmunized pregnancies and in women with immune thrombocytopenia after appropriate counseling.

Clinical findings and the results of rapid karyotype for fetuses with three categories of structural malformations are shown in Tables II, III, and IV. Five of 18 fetuses with these structural malformations had chromosomal abnormalities, an incidence of 27.7%. Clinical findings and the results of rapid karyotype in fetuses with IUGR or oligohydramnios are listed in Table V. Three of 13 fetuses with IUGR had chromosomal abnormalities, an incidence of 23.1%.

Comment

The high incidence of chromosomal abnormalities in fetuses with structural malformations is emphasized by our data. Cordocentesis was helpful to obtain rapid karyotype. The finding of abnormal karyotypes in one of seven fetuses with renal or urinary tract abnormalities emphasizes the need to obtain fetal karyotype before any therapeutic shunt procedure is planned. Such procedures have been reported[9] with mixed results. Two of the four cases (Table II) with sonographic features of obstructive uropathy underwent shunt procedures. One procedure was unsuccessful and the patient chose to terminate the pregnancy. The other shunt procedure was successful, but the infant had early neonatal death. One pregnancy was terminated, and one pregnancy resulted in delivery of an infant with bilateral hydronephrosis who is currently doing well at age 20 months.

The increased incidence of chromosomal abnormalities in pregnancies complicated by omphalocele has been emphasized in a previously reported prenatal study.[10] Two of four cases in our study were revealed to have chromosomal abnormalities. Because omphalocele can be corrected postnatally with immediate surgery, but trisomy 18–monosomy 13 can be potentially lethal, the information obtained on fetal karyotype was critical in management decisions with regard to these cases.

Single umbilical artery has been recognized[11] as associated with a high incidence (33.3%) of chromosomal abnormalities. However, this finding is not commonly recognized as an indication to obtain karyotype. Our cases substantiate the previous report and highlight the need for careful evaluation of umbilical cord at obstetric sonography.[12]

Perinatal outcome in pregnancies complicated by

Table V. Findings of IUGR-oligohydramnios cases

No.	*Clinical findings*	*Gestational age (wk)*	*Karyotype*
1	IUGR-oligohydramnios	24	Normal
2	IUGR-oligohydramnios	31	Normal
3	IUGR-oligohydramnios	28	Normal
4	IUGR-oligohydramnios	37	Normal
5	Oligohydramnios	25	Normal
6	Oligohydramnios	20	Normal
7	Oligohydramnios	21	Normal
8	IUGR	30	Normal
9	IUGR	31	Normal
10	IUGR	31	46,XX,15q−
11	Oligofacial dysmorphic features	32	Normal
12	IUGR-gastrointestinal obstruction	26	69,XXY
13	IUGR-oligohydramnios, hydronephrosis	36	47,XX+21

early IUGR and severe oligohydramnios is extremely poor. If severe oligohydramnios is present without significant IUGR, a diligent search should be made to rule out leakage of amniotic fluid. Careful sonography should be performed to detect any associated structural malformations, but such examination may be hindered by poor visualization because of a lack of fluid. Fetuses with early IUGR or severe oligohydramnios are at increased risk of toxoplasmosis, rubella, cytomegalovirus, and herpes simplex infections, chromosomal abnormalities, and hypoxemia. Evaluation for these parameters can be carried out by obtaining pure fetal blood by cordocentesis. Improved neonatal survival has encouraged obstetricians to intervene for fetal indications at earlier gestational ages. Therefore information on fetal karyotyping is critical in planning management.

As presented in this article, all fetal structural malformations and early cases of IUGR or severe oligohydramnios should be recognized as indications for karyotyping the fetus. This raises a significant dilemma because the majority of these cases are recognized at an advanced gestational age, therefore the option for termination of pregnancy may not be available to the patient. Accordingly, all patients should receive appropriate counseling including discussion of available options before undergoing procedures for the purpose of fetal karyotyping. In our opinion, the primary benefit derived from such testing lies in careful planning of management as it relates to whether cesarean section for fetal distress should be performed. Uniformly lethal chromosomal abnormalities such as trisomy 13 or 18 may be contraindications for performance of cesarean delivery for fetal indications.

Severely isoimmunized pregnancies are very high-risk gestations, frequently requiring transfusion therapy. The finding of one abnormal karyotype of 12 cases highlights the importance of incidental karyotyping of the fetus at the first cordocentesis performed in any isoimmunized pregnancy. Incidental karyotype may also be important in discordant twin gestations, especially if any structural malformation is recognized, as exemplified in our case of monozygotic twins with trisomy 18.

In summary, cordocentesis is helpful to obtain rapid karyotype in cases of fetal structural malformations, IUGR, and nonimune hydrops fetalis, and also may be useful for incidental karyotyping in isoimmunized pregnancies and discordant twin gestations. The karyotype information thus obtained is further helpful in planning clinical management.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Kenneth J. Moise, Jr., Houston, Texas. Since the introduction of the technique of fetal blood sampling by Daffos in France in 1983, cordocentesis has gained widespread acceptance. Although Daffos first used the procedure in the detection of intrauterine fetal infection, further study has revealed the technique to be very useful in other clinical situations in which access to the fetal vascular space is necessary. Data from the

1987 U.S. registry for fetal blood sampling reveals that the predominant indications for the procedure in this country are red cell alloimmunization and cases of chromosomal mosaicism detected by chorionic villus sampling (CVS) or amniocentesis. The authors of the current manuscript have shown a series of cordocenteses for rapid fetal karyotype determination.

My major concern with the manuscript is that the authors fail to address the issue as to when cordocentesis should be used to obtain a rapid fetal karotype. In most centers a fetal karyotype can be obtained by lymphocyte culture within 48 hours. In addition, new culturing techniques for amniotic fluid will produce karotype results in 10 to 14 days. Finally, a direct preparation of chorionic villi obtained by transabdominal CVS will produce karotype results the same day the procedure is undertaken. Rapid karyotype seems to be necessary in two clinical situations. Detection of a fetal anomaly or presentation of a patient at risk of chromosomal abnormalities just before the gestational age at which legal termination of pregnancy can be undertaken represents the first indication for rapid karotype analysis. In this situation, chromosomal analysis obtained by amniocentesis would not return soon enough for the patient to use these results to decide whether to continue a pregnancy. The second indication for rapid karyotype is a situation in which the patient is first seen with fetal anomalies late in the third trimester, when knowledge of an abnormal karyotype would influence obstetric management. Again in this situation, results obtained by amniocentesis may not return before the onset of labor or the detection of fetal distress. An example would be a patient with a newly diagnosed omphalocele at 36 weeks' gestation. If trisomy 18 was found in association with this omphalocele, a vaginal delivery would be preferred.

In Table II of the current manuscript, only one case of renal anomaly was seen at 22 weeks' gestation that may have necessitated fetal blood sampling for rapid chromosome analysis. In addition, two of the eight patients were first seen after 35 weeks' gestation when a karyotype may have influenced obstetric intervention. In Table III, only one of seven patients was first seen at >35 weeks' gestation. In Table IV, none of the four fetuses with umbilical cord abnormalities were first seen at a point in pregnancy when rapid fetal karyotype was necessary for management. Finally, in Table V, only two fetuses were first seen at >35 weeks' gestation. I pose several questions to the authors. First, was transabdominal CVS considered in any of these cases to obtain a rapid karyotype within 24 hours? Second, inasmuch as amniocentesis has a loss rate of approximately 0.5% to 1%, whereas umbilical blood sampling has been reported to have a loss rate from 0.5% to 3.8%, why did the authors chose to use a riskier procedure when in the majority of their cases a rapid karyotype was probably not necessary? What was the authors' loss rate related to cordocentesis in the current series?

My second concern with the presentation involves the recommendation by the authors that fetal blood obtained for other indications such as platelet assessment in the case of immune thrombocytopenic purpura or fetal hematocrit in the case of the alloimmunized pregnancy should be sent for rapid karyotype. One patient of 12 alloimmunized pregnancies was noted to have a chromosomal abnormality. What was the result of this karyotype analysis? Did this patient have any other risk factors that would identify an increased risk for chromosomal abnormalities? Do the authors await the chromosome analysis if fetal thrombocytopenia is detected at cordocentesis before effecting delivery in the pregnant patient with immune thrombocytopenic purpura?

In summary, fetal blood sampling is a useful tool that enables the perinatologist to directly assess the fetal hematologic environment. Rapid karyotype analysis can be undertaken in certain clinical situations when the obstetric decision-making process is influenced by the finding of an abnormal karyotype. To recommend cordocentesis for karyotype analysis at *any* gestational age when a fetal anomaly is detected would appear to be an overutilization of this new and exciting technique.

Dr. Washington Hill, Omaha, Nebraska. I guess the real question for perinatologists and for the physicians in the community is when should the patient be referred for cordocentesis? I would like Dr. Shah to go over that one more time.

Dr. Robert J. Carpenter, Houston, Texas. The issue in this manuscript, which was to have been the main question in doing a rapid karyotype, was the potential benefit. If one takes away the 10 cases of discordant twins, the 12 cases of isoimmunization, six immune thrombocytopenic purpura, and the five others as defined, that removes 33 patients from the series of 101 patients. That then increases to approximately 18% the total positive pickup. That point was not addressed.

Dr. Sharon L. Dooley, Chicago, Illinois. I want to congratulate Dr. Shah on a very nice series. Just to expand a little bit on the safety issue, as our experience with cordocentesis increases our fetal loss rate is going to drop. It is starting to look fairly favorable compared with amniocentesis. However, we should remember that the amniocentesis loss rate that we quote, namely 0.5%, is based on early second-trimester amniocentesis. The risk of a later pregnancy amniocentesis is far lower than that.

Dr. Daniel A. Rightmire, Springfield, Illinois. Are there data that address the frequency with which the 8- to 10-day difference between rapid karyotyping from fetal blood sampling and from amniocentesis has proved to be of benefit to the patient or the physician? That is really the issue in rapid karyotyping.

Dr. Judith A. Ney, Rochester, Minnesota. It seems to me that the loss rate is certainly crucial here and the questionable clinical usefulness of rapid karyotyping at these gestational ages has been commented on, but the other issue is the morbidity of the procedure. How many of these patients required emergency cesarean section at a gestational age of 26 weeks because the procedure was performed?

Dr. Shah (Closing). Dr. Moise and the various members have raised some very pertinent questions.

As to the question of transabdominal CVS in these cases that were subjected to rapid karyotyping, I think one should keep in mind that not all cases are amenable to CVS and that cordocentesis may be an easier procedure. This would be an issue in cases with posterior placentas, all the more so if there is the presence of oligohydramnios or structural malformation that may interfere. Also, we do not have an ongoing program of transabdominal CVS. However, it must be added to the armamentarium available to the perinatologist for patients who may require rapid karyotyping.

As far as electing to perform cordocentesis for rapid karyotyping over amniocentesis is concerned, several issues need to be addressed. First, many of these patients are referred to our center not necessarily for cordocentesis but for other clinical circumstances, including preterm labor or severe fetal heart rate abnormalities. Adjunctive indications for obtaining fetal blood may exist, such as gas analysis or typing of human leukocyte antigen for diagnosis of zygocity. In cases of preterm labor the need to obtain the fetal karyotype results in a shorter time is heightened.

I think it is important that patients for whom such clinical circumstances are not present be offered all the diagnostic options available to them, including amniocentesis. This was done in all cases by a genetic counselor (who is also the coauthor of the manuscript) who independently counseled all the patients and offered them the option of amniocentesis.

It is interesting to note that the majority of the patients nevertheless accepted rapid karyotyping by cordocentesis over amniocentesis. This may be essentially a reflection of anxiety on the part of the mother who has not only discovered that there is another perinatal problem, but that a serious fetal abnormality or other concerns may be present.

As far as the risk/benefit ratio is concerned, amniocentesis is considered as having a $\leq 0.5\%$ risk when performed in the third trimester. Even so, it is offered in certain cases in which the chance of finding an abnormal karyotype is very low. If one were to readjust the data and selectively address the issues of fetal structural malformations, IUGR, nonimmune fetal hydrops, discordant twins, and advanced gestational-maternal age, one gets numbers as follows: 78 cases with 11 abnormal karyotypes, for an abnormal karyotyping incidence of 13.7%. This certainly would be significant in the patient's decision-making process and should enter into the counseling process as far as the risk/benefit ratio is concerned.

As far as the case of isoimmunized pregnancy is concerned, I have already addressed the results of the karyotype. This fetus did not have other structural malformations detected on careful sonographic examination. The results of the rapid karyotype returned as mosaic 45,X/46,X, ring form X as previously stated, essentially a 45,X or X monosomy. The patient was counseled about the results, and after counseling with regard to the outcome of this fetus, also underwent intrauterine fetal transfusions as indicated for the isoimmunized process. We do not consider isoimmunization per se as an indication to obtain karyotyping. However, before embarking on complex and invasive management, consideration should be given to assuring the chromosomal normalcy of the fetus.

As far as the cases of immune thrombocytopenia are concerned, many of these patients were referred into our center; and the cesarean delivery was planned adequately remote from the time of the cordocentesis. Rapid karyotyping was performed from a sample of convenience, and we do not advocate this for routine management.

With regard to the question by Dr. Hill as to when clinicians should refer patients for cordocentesis, my response is that clinicians should refer patients for primary clinical considerations, which are the usual common perinatal conditions that require referral, such as premature labor and fetal structural malformations. I think the decision as to what diagnostic options should be offered to the patient is best left in the hands of the people who counsel these patients and offer all the options on a routine basis and therefore are better able to explain to the patient the various considerations involved in these cases. Therefore, I do not have any specific list of indications for which physicians should refer patients for cordocentesis.

However, the cases presented here heighten concerns with regard to many of the fetal structural malformations, an example being the single umbilical artery. Even though this malformation was recognized previously to be associated with chromosomal abnormalities, it is not usually addressed in a sonography report. I believe it should be addressed routinely in a sonography report so that this information can be used in management.

Dr. Carpenter's comments about higher pickup rate are very pertinent if we consider only the population with specific indications. If we eliminate 23 samples of convenience, then the 78 patients with specific indication had 11 abnormal test results, a rate of 13.7%.

As far as Dr. Dooley's question with regard to the risks of amniocentesis is concerned, I agree with her that the risk of amniocentesis in our hands is far less than what is commonly cited from the literature or from the U.S. collaborative data. In the third trimester the risk would be expected to be even lower, and this should be explained to the patient as far as her diagnostic options are concerned.

In response to Dr. Rightmire's question with regard to the primary benefit to the patient, I think all the issues that we discussed, in terms of having knowledge about the normal karyotype and appropriately preparing the mother for the possibility of abnormal karyotype results and their influence on clinical decision making, are important considerations.

With regard to the question of morbidity in these cases and the question of fetal loss rate that Dr. Moise raised, there was one fetal loss in this total group of

101 cases. This was a case at 17 weeks' gestation with severe oligohydramnios and suspected renal agenesis. The patient also underwent instillation of indigo carmine dye and had a tetanic uterine contraction with rupture of membranes. This fetus was the only one lost in this series. The patient subsequently elected to complete the process of abortion with prostaglandin.

As far as the question of morbidity is concerned, there was not a single case of fetal distress or emergency cesarean section that was related to the procedure itself in this series.

The effect of prolactin on murine in vitro fertilization and embryo development

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Elevated levels of serum and follicular fluid prolactin occur in women undergoing ovulation induction with both clomiphene citrate and gonadotropin therapy. Prolactin's effect on oocyte fertilization and embryo cleavage has not been fully characterized. Using a murine model, we investigated the effect of prolactin on in vitro fertilization and subsequent embryo cleavage in media containing 150, 400, and 600 ng/ml purified mouse prolactin. No difference was found in fertilization rates when compared with control rates. Culture of both in vivo and in vitro fertilized two-cell embryos in murine prolactin at 150, 400, and 600 ng/ml showed no significant difference in blastocyst, morula, or embryo degeneration rates when compared with control rates. An assay for binding of murine prolactin to spermatozoa, oocytes, and the embryo at various cleavage stages revealed no specific murine prolactin binding. These in vitro experimental results fail to show a role for murine prolactin in effecting mature oocyte fertilization or subsequent embryo cleavage. The lack of binding of murine prolactin to the gametes and early developing embryo supports the in vitro findings. (Am J Obstet Gynecol 1990;162:1553-61.)

Key words: Prolactin, in vitro fertilization, embryo cleavage

The mammalian oocyte enters the first meiotic division and arrests in diplotene prophase during fetal life. Oocytes remain in the dictyate stage until shortly before ovulation when meiotic competence is obtained and the first meiotic division is completed. A large amount of experimental data supports the primary importance of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin as major regulators of follicle development and oocyte maturation.

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Prolactin has been shown to have an inhibitory effect on both rat and human granulosa cell estrogen and progesterone synthesis.[1, 2] In addition to its action on granulosa cell estrogen and progesterone synthesis, ovine prolactin has been found to stimulate granulosa cell production of oocyte maturation inhibiting factor.[3] One study indicates that oocyte maturation inhibiting factor may in fact be an enzyme-clipped oligopeptide fragment of prolactin.[4] Through its modulating action on estrogen and progesterone synthesis and oocyte maturation inhibiting factor activity, prolactin probably plays a significant role in oocyte maturation. Its role, if any, in fertilization and early embryo development is less well defined.

Several investigators have examined follicular fluid human prolactin levels in women undergoing ovulation induction for in vitro fertilization and have found that lower mean levels are positively associated with oocyte fertilization.[5, 6] In contrast, other studies correlated higher follicular fluid human prolactin levels in preovulatory follicles with oocyte fertilization.[7, 8] Another

study measured bioactive follicular fluid human prolactin levels by use of an Nb2 lymphoma cell bioassay together with immunoreactive human prolactin levels and found no correlation between bioassay or immunoreactive follicular fluid human prolactin levels and oocyte fertilization.[9]

Murine in vitro fertilization and embryo development experiments with prolactin have yielded equally conflicting reports. An initial study indicated that ovine prolactin, at a level of 100 ng/ml, inhibited in vitro progression of murine two-cell embryos to blastocyst.[10] A subsequent study, evaluating murine prolactin levels up to 100 ng/ml, failed to find any effect of murine prolactin on two-cell embryo to blastocyst development in vitro.[11] However, these authors reported that when spermatozoa were incubated with culture media supplemented with 100 ng/ml of murine prolactin, there was a reduction of in vitro fertilization capacity. With the recognition that mouse serum prolactin levels of 100 ng/ml represent low estrous levels, a more recent study evaluated ovine prolactin levels up to 1000 ng/ml.[12] This group reported improved in vitro mouse two-cell embryo to blastocyst development with supraphysiologic ovine prolactin media supplementation.

The purpose of our study was to evaluate the in vitro effect of murine prolactin on fertilization and subsequent embryo development with a homologous murine model. This study was designed to examine physiologic and supraphysiologic murine prolactin effects. Additionally we investigated spermatozoa, oocytes, and the preimplantation embryo for specific murine prolactin binding.

Material and methods

Animals. Sexually mature CB6F1 female mice, 8-12 weeks of age (Charles River Laboratories, Wilmington, Mass.) were used in both the in vivo and the in vitro fertilization experiments. The CB6F1 mouse is a hybrid cross between BALB/c and C57B1/6 strains. Oocytes from this hybrid F1 mouse have consistently provided in vitro fertilization rates of 70%. Individually housed 4- to 6-month-old CB6F1 male mice (Charles River Laboratories) were used in all experiments. Ovulation induction was carried out in standard fashion with female mice receiving 5.0 IU of pregnant mare serum gonadotropin (Sigma Chemical Co., St. Louis) intraperitoneally followed by 5.0 IU of human chorionic gonadotropin (hCG) (Sigma Chemical Co.) intraperitoneally 48 hours later.

Culture media. Fresh Whitten's medium was prepared as described elsewhere for both fertilization and embryo culture.[13] The medium was adjusted to an osmolarity of 278 ± 2 mOsm/L. Whitten's medium used for in vitro fertilization was supplemented with 30 mg/ml bovine serum albumin (ICN Immunobiologicals, Lisle, Ill.). Whitten's medium that was used for embryo culture (designated as the growth medium) was supplemented with 3 mg/ml bovine serum albumin. The fertilization and growth media were adjusted to a pH of 7.4 after equilibration in a 5% carbon dioxide–air incubator at 37° C. All media were filter sterilized immediately before use. In vitro fertilization and embryo cultures were carried out in 60 × 15 mm welled Falcon culture dishes (Becton Dickinson & Co., Oxnard, Calif.) in a humidified 5% carbon dioxide–air incubator at 37° C.

Purified murine prolactin in lyophilized form was graciously provided by Dr. A. F. Parlow, Director of the Pituitary Center at Harbor–University of California Los Angeles Medical Center. A fresh stock solution of murine prolactin was made for each experiment by dissolving 10.0 μg of the murine prolactin in 5 ml of Whitten's growth medium.

In vitro fertilization. Female mice were put to death by cervical dislocation 14 to 16 hours after hCG injection. The cumulus masses were dissected from the oviducts and immediately placed in Whitten's fertilization medium. A minimum of eight female animals were put to death for each experiment to provide sufficient oocytes to simultaneously test each concentration of murine prolactin. Cumulus masses were pooled and randomly assigned to the different murine prolactin test concentrations or unsupplemented control fertilization media. One cumulus mass was cultured per welled Falcon culture dish. For each experiment there were four culture dishes each for control and 150, 400, and 600 ng/ml murine prolactin test concentrations. The in vitro fertilization experiments were repeated three times and results were pooled for analysis. The murine prolactin concentrations studied were based on results of serum murine prolactin levels that we have assayed in this strain of mouse. We found that CB6F1 female mice had a mean estrous prolactin level of 124 ± 32 ng/ml (range 78 to 180) while pregnant mare serum gonadotropin– and hCG-stimulated mice had a mean serum prolactin level of 220 ± 83 ng/ml (range 102 to 450). Prolactin concentrations were set at 150, 400, and 600 ng/ml to test prolactin at normal physiologic, ovulation induction, and supraphysiologic levels.

Male mice were put to death by cervical dislocation. The caudal epididymides were removed and placed in Whitten's fertilization medium. Sperm was extruded from each epididymis by gently squeezing the epididymis with watchmen forceps. The sperm suspensions were immediately placed in the 5% carbon dioxide–air incubator at 37° C. Sperm suspensions were examined at 10 minutes for the presence of whirlpool-like formations on the surface. Sperm count and motility were

assessed immediately before insemination of dishes. Approximately 0.5 × 10^6 motile sperm was added to each fertilization dish, which contained 10 to 20 oocytes. Ova and sperm were incubated together for 6 hours in control or murine prolactin–supplemented fertilization dishes containing 150, 400, or 600 ng/ml of murine prolactin. At the end of 6 hours the oocytes were washed twice and transferred to growth media supplemented at the same murine prolactin concentration as that in the respective fertilization media. All morphologically abnormal oocytes were discarded. This represented between 5% and 10% of oocytes collected. Dishes were examined at 24 hours for fertilization (defined at the two-cell stage). For each murine prolactin test level the even-two-cell embryos were then randomly divided, with half transferred to growth media of similar murine prolactin concentration while the other half were transferred to unsupplemented growth media. At 96 hours the numbers of blastocysts, morulas, two-to-eight cell embryos, and degenerated embryos were recorded. For each concentration of murine prolactin 126 to 188 oocytes were tested.

In vivo fertilization. Female mice were caged with male mice of proved fertility after receiving an hCG injection at 4 PM. In the morning mating was confirmed by observation of a vaginal plug. The female mice were removed from the mating cages and housed together. Female mice were put to death by cervical dislocation 48 hours after hCG administration. Two-cell embryos were collected from the dissected oviducts with abnormal embryos discarded. Abnormal embryos, including degenerating and uneven two-cell embryos, represented between 5% and 10% of all embryos. The two-cell embryos from six to eight female mice were pooled and randomly distributed. Experiments were run in parallel fashion with 0, 150, 400, and 600 ng/ml of media supplemented with murine prolactin. Embryos were transferred to fresh media every 24 hours. After 72 hours the numbers of blastocysts, morulas, two-to-eight-cell embryos, and degenerated embryos were recorded. The in vivo fertilization experiment was performed on three separate occasions to achieve a minimum of 75 even-two-cell embryos included for each group tested.

Radioiodination and binding of mouse prolactin. Purified murine prolactin (AFP 6476C) was radioiodinated by use of iodogen (Pierce, Rockford, Ill.) as previously described (30 μCi/μg).[14] Specific binding of murine prolactin labeled with iodine 125 to gametes was evaluated by the addition of 100,000 cpm of labeled murine prolactin to gametes or embryos in the presence or absence of a 100-fold excess of unlabeled murine prolactin. Approximately 50,000 spermatozoa and 100 oocytes and embryos at the two-cell, four-to-eight-cell, morula, and blastocyst stages each were tested. Incubations were done in 25 μl of phosphate-buffered saline solution containing 0.1% bovine serum albumin. After 2 to 4 hours at 37° C, the incubation was terminated by the addition of 2 ml of cold phosphate buffered saline solution and centrifugation. The supernatant was aspirated, and the precipitate was washed and counted. Specific binding was defined as those counts that were displaced by the addition of unlabeled murine prolactin. As a positive control, iodinated murine prolactin was incubated with a preparation of rat liver membrane in the presence or absence of excess unlabeled murine prolactin.

Statistical analysis. Transformation rates of in vivo fertilized two-cell embryos to blastocysts were analyzed by χ^2 test. In vitro fertilization rates between groups were also analyzed by χ^2 test. Log linear analysis was used for three-dimensional contingency table comparison of embryo development from the in vitro fertilized oocytes as a function of the different murine prolactin concentrations and time of murine prolactin exposure.

Results

In vivo fertilization. The effect of increasing concentrations of murine prolactin on two-cell embryo to blastocyst transformations and percent degeneration is shown in Fig. 1. Blastocyst formation determined at 72 hours in the control group was 70%, while embryo degeneration rate was 14%. As seen in Fig. 1, embryos exposed to 150, 400, and 600 ng/ml murine prolactin had blastocyst transformation and embryo degeneration rates similar to those of the control group. There was no significant difference in the embryo development profile when blastocyst, morula, two-to-eight-cell, and degenerated embryo transformation rates of test murine prolactin concentration groups were compared with control rates.

In vitro fertilization. Oocytes were exposed to physiologic and supraphysiologic levels of murine prolactin during the time of fertilization and subsequent embryo development. These were compared with unsupplemented controls. The fertilization rate defined at the two-cell cleavage stage was 73% in the control group. Table I summarizes the fertilization rates for the study and control groups. As can be seen, there was no statistically significant difference in fertilization rates between the murine prolactin and control groups. Fig. 2 summarizes the subsequent embryo development of the in vitro fertilized oocytes. As depicted in Fig. 2, the rate of blastocyst transformation and embryo degeneration was similar between the initial 24-hour-only and 96-hour murine prolactin exposure groups and control. A comparison of development of all embryos was made by categorizing stage of development into blastocyst, morula, two-to-eight-cell embryos, and degenerated

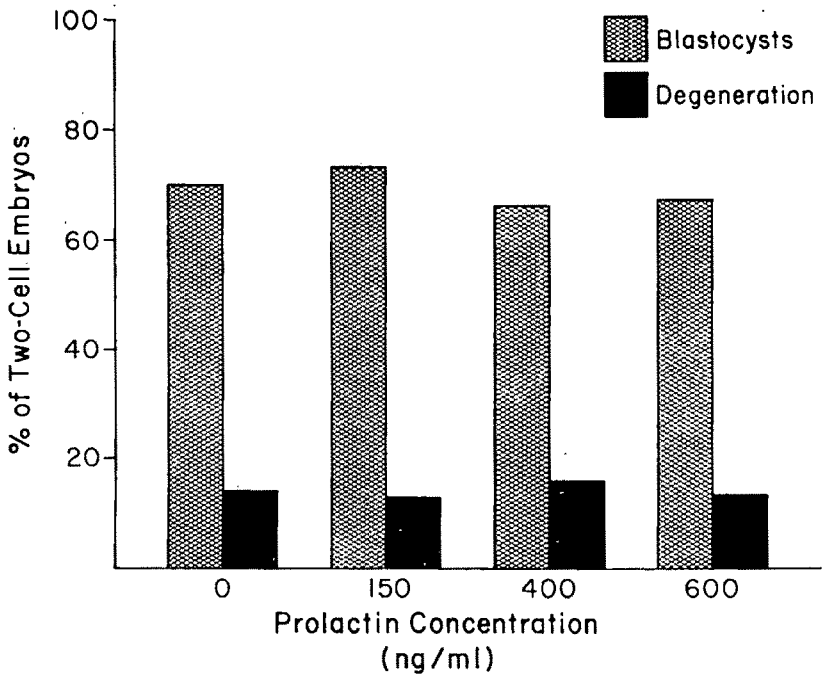


Fig. 1. Effect of murine prolactin on the development of mouse oocytes fertilized in vivo. Two-cell embryos in test groups were cultured in murine prolactin–supplemented media for 72 hours.

Table I. Effect of marine prolactin on in vitro fertilization rates

Prolactin concentration (ng/ml)	*Fertilized*		*No. of oocytes*
	No.	*%*	
0	120	73	165
150	86	68	126
400	134	71	188
600	91	68	133

embryos. Log linear analysis revealed no statistical difference in these stages of embryo development between 24-hour murine prolactin, 96-hour murine prolactin, and control groups.

Binding of murine prolactin. There was no specific binding to spermatozoa, oocytes, or embryos. On incubation with 100,000 cpm of murine prolactin labeled with ^{125}I, between 5% and 15% of the radioactivity was associated with the cells at the end of the incubation. However, the percentage was not altered by the addition of a 100-fold excess of unlabeled murine prolactin. The rat liver membrane preparation was found to specifically bind 27% of the labeled murine prolactin.

Comment

Clinical studies evaluating follicular human prolactin levels in women undergoing in vitro fertilization have yielded conflicting results concerning follicular fluid human prolactin concentration and its relationship to oocyte fertilization.[5-8] Two studies reported a negative association between follicular fluid human prolactin levels and oocyte fertilization.[5,6] In contrast, other studies found that high follicular fluid human prolactin levels seemed to correlate with oocyte fertilization.[7,8] Studies evaluating the effect of ovine prolactin and murine prolactin on mouse in vitro two-cell embryo to blastocyst progression have also revealed conflicting results.[10,12] To our knowledge, this study represents the first in vitro study of physiologic and supraphysiologic murine prolactin concentrations on in vitro fertilization and subsequent embryo development. The results reported here suggest no significant effect of murine prolactin at physiologic or supraphysiologic levels on mouse in vitro fertilization or subsequent embryo development. The murine prolactin concentrations, as stated earlier, reflect the physiologic range of serum murine prolactin levels seen during estrus in CB6F1 mice (78 to 180 ng/ml), during pregnant mare serum gonadotropin stimulation in this strain (102 to 450 ng/ml) and the supraphysiologic range (600 ng/ml). While serum prolactin levels do not necessarily reflect prolactin concentrations in the fallopian tube, there have been several human studies demonstrating the close correlation between follicular fluid and peritoneal fluid human prolactin compared with serum concentrations.[15,16] Since the mouse fallopian tube encapsulates its ovary, it was felt that if serum and follicular fluid murine prolactin levels are closely approximated,

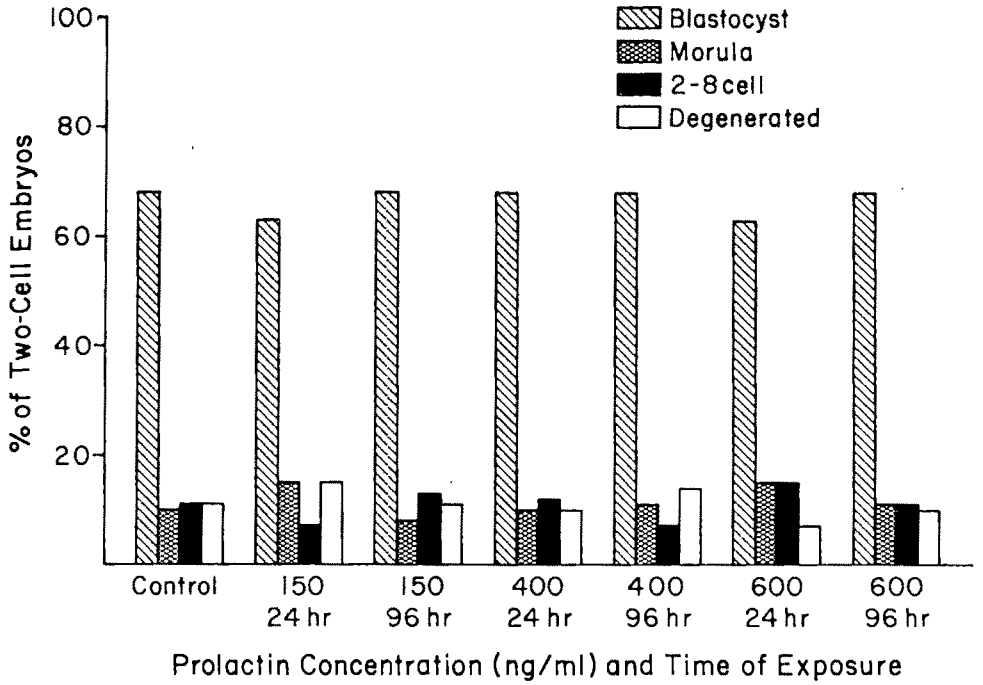


Fig. 2. Effect of murine prolactin exposure on embryo development from oocytes fertilized in vitro. Oocytes were fertilized in murine prolactin–supplemented media. At 24 hours half the fertilized two-cell embryos were transferred to unsupplemented Whitten's media with the other half transferred to fresh murine prolactin media. At 96 hours both 24-hour and 96-hour murine prolactin exposure groups were evaluated.

as is seen in humans, then the murine prolactin concentration in the fallopian tube would probably also approximate the serum concentration after follicle rupture.

The lack of any in vitro inhibitory or stimulatory effect of purified murine prolactin on fertilization or two-cell embryo to blastocyst development suggests that, in the mouse, murine prolactin has no direct postovulatory effect on the oocyte or early embryo. These findings differ critically from those of Fukuda et al.[11] and Yohkaichiya et al.[12] Yohkaichiya et al.[12] reported an improved in vitro rate of blastocyst and hatched blastocyst development from in vivo fertilized mouse embryos when cultured in ovine prolactin concentrations of 100 to 1000 ng/ml.[12] However, the blastocyst transformation rate in their study was unusually low in both the supplemented media control group (20%) and the test groups with ovine prolactin concentrations <100 ng/ml (20%), making interpretation difficult. Additionally they tested ovine prolactin rather than murine prolactin. As reported here Fukuda et al.[11] found no effect of murine prolactin on mouse two-cell embryo to blastocyst development; however, they reported a decrease in the in vitro fertilization rate when spermatozoa were preincubated in culture media containing 50 and 100 ng/ml murine prolactin concentrations. In their study Fukuda et al.[11] defined fertilization at the male pronuclei level and not at the two-cell cleavage stage. They found no difference from control in the motility rates of epididymal spermatozoa preincubated with murine prolactin and had no explanation for the decreased in vitro fertilization capacity of these spermatozoa. In our experiment spermatozoa were first preincubated in unsupplemented media and then combined with fresh oocytes in control or murine prolactin–supplemented fertilization media. In this setting we found no in vitro effect of murine prolactin on the spermatozoa's fertilization capacity as defined at the two-cell cleavage stage.

Consistent with our in vitro results, we found no evidence of murine prolactin binding to spermatozoa, the oocyte, or the early embryo. It must be acknowledged that the radiolabeled murine prolactin assay used for receptor detection is probably not sufficiently sensitive to detect receptors at low concentrations. Experiments with more sensitive receptor analysis techniques would be needed to evaluate the possibility of a low number of murine prolactin receptors on either the gametes or early embryo.

Clearly prolactin has been shown to be an important gonadotropin regulator of ovarian follicle development. It is well known that hyperprolactinemia can disrupt ovarian follicle development and corpus luteum function, resulting in menstrual cycle disorders

including luteal phase defect, anovulation, and infertility.[17] Centrally prolactin increases hypothalamic dopaminergic and opioid tone, which may affect LH and FSH secretion by inhibiting pulsatile secretion of gonadotropin-releasing hormone.[18] Prolactin also has direct ovarian actions that include inhibition of FSH-induced aromatase activity in rat granulosa cells[19] and in vitro suppression of progesterone production from human granulosa cells.[1] Of potentially greater significance, Channing and Evans[3] have shown that ovine prolactin will stimulate in a dose-dependent fashion porcine granulosa cell release of the nonsteroidal oocyte maturation inhibition factor. The role of prolactin in maintenance of meiotic arrest has been further substantiated in studies by Baker and Hunter[20] and Nolin.[4, 21] Baker and Hunter[20] have demonstrated that antiprolactin serum induced oocyte meiotic maturation in cultured porcine follicles. Subsequently Nolin[21] demonstrated the presence of rat prolactin in both granulosa cells and the dictyate oocyte. Nolin[4] noted that the availability of rat prolactin for oocyte uptake was dependent on transcellular transport from the granulosa cell, probably via the thin processes that project from cumulus cells through the zona pellucida to contact the oolemma at gap junctions. With anti–rat prolactin antisera, molecular homology between purified pituitary rat prolactin and oligopeptides in Channing's oocyte maturation inhibition factor follicular fluid fraction also has been demonstrated. Nolin[4] hypothesized that the role of prolactin in maturation inhibition may be analogous to a corticotropin-like intermediate lobe peptide theory of peptide hormone action in which prolactin acts as a parent polypeptide that undergoes cleavage by target cell proteases into small oligopeptide fragments, which are the responsible agents in the inhibition of maturation. Since cumulus cells in mice, as well as humans, remain in contact with the oocyte during fertilization, it seemed clearly possible that prolactin or an oligopeptide fragment of prolactin also may act in a regulatory fashion after ovulation to affect oocyte fertilization or early embryo cleavage. It was for this reason that we felt it important to study cumulus-intact mouse oocytes.

The lack of an in vitro effect of murine prolactin on fertilization and early mouse embryo development does not eliminate the possibility of an in vivo role. Osmoregulatory actions of prolactin in euryhaline fish, in the chick embryo, and in transport of water across the human amnion are well known. It may be that prolactin acts in an osmoregulatory fashion at the level of the fallopian tube and endometrium to maintain the proper milieu for fertilization and embryo development. It is also possible that in vivo prolactin gives rise to regulatory oligopeptides within the fallopian tube or at the level of the endometrium that could affect in vivo fertilization, embryo development, or implantation. The present in vitro study cannot rule out these possibilities.

In conclusion, this study demonstrates that murine prolactin at physiologic and supraphysiologic levels had no adverse effects on in vitro fertilization and embryo development in the mouse. The absence of murine prolactin receptors on the gametes and early embryo is consistent with these findings. Species differences with respect to prolactin action on gametes and/or early embryo development may clearly exist. However, recent clinical studies in women undergoing in vitro fertilization procedures also support no effect of elevated serum prolactin levels on subsequent in vitro fertilization, embryo cleavage, or pregnancy rate.[22] In addition, human amniotic fluid with its known high human prolactin concentration has been successfully used as fertilization and embryo growth media for both mouse and human in vitro fertilization.[23] These data further corroborate the findings in our study. It should be cautioned that our study did not address the potential negative effect of oocyte exposure to elevated midcycle prolactin levels before ovum release. Further characterization of the actions of prolactin as a reproductive hormone will require investigation of potential in vivo effects of prolactin on embryo development, tubal transport, and implantation.

We thank Dr. Larry Sachs for his assistance with the statistical analysis.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Marguerite K. Shepard, Indianapolis, Indiana. The effect of elevated levels of prolactin on ovarian function in regularly cycling women has been a source of investigation for some years. While initial reports associated hyperprolactinemia with luteal phase abnormalities,[1] subsequent studies have shown that prolactin affects follicular phase events as well. Not only the pattern of follicle development is affected by prolactin levels[2] but also intrafollicular events such as aromatase activity[3] and LH receptor formation.[4] Conflicting reports on the effect of systemic and follicular fluid levels of prolactin on the outcome of in vitro fertilization cycles have led to this study. In a broader sense this article addresses the role of prolactin in the immediate postovulatory phase of the cycle.

Dr. Dodds and his co-workers have specifically investigated the direct effect of prolactin on gametes, the fertilization process, and early embryonic development on the CB6F1 mouse. This strain was chosen because it is used commonly to test culture medium for use in human in vitro fertilization. They have attempted to correct the deficiencies noted in previous studies by continuing their cultures through the immediate preimplantation phase of embryonic development. They have included embryos from both in vivo and in vitro fertilization to control for the effects of fertilization environment on embryonic development, and a crossover segment addresses the effect of prolactin in the tubal fluid on the development of preimplantation embryos. Their successful fertilization rate is in the range reported for the CB6F1 mouse.

Their study design includes adequate numbers of observations of each time point for meaningful data to be accumulated. The time period encompassed by the study includes the postovulatory, preimplantation phase of the cycle when the effect of elevated prolactin would necessarily be a direct one on the gametes and embryos rather than on the support system, including the follicle, the corpus luteum, and the endometrium.

Their results consistently fail to demonstrate any direct effect of prolactin in the fluid medium surrounding the gametes and developing embryos on the fertilization rate or subsequent embryo development when compared with controls.

The major problem in extrapolating these data to normal periovulatory events is the lack of a control group involving unstimulated mice or a mouse strain that does not show a physiologic rise in prolactin at the midcycle. Cutie and Andino,[5] using cultured human granulosa cells, have shown a threshold effect of prolactin on inhibition of FSH-mediated steroid biosynthesis with no further inhibition with increasing levels of prolactin. Since all of the mice were pregnant mare serum gonadotropin–hCG stimulated, all oocytes were presumably exposed to an elevated level of endogenous prolactin before retrieval. Would the fertilization rate have been higher than 70% if such exposure had not occurred or if exposure to lower levels of endogenous prolactin had occurred as seen in spontaneous cycles?

The absence of prolactin binding to the gametes or embryos may answer this question, but as the authors point out, their techniques don't eliminate the possibility of low-level receptor formation.

The extrapolation of these data to human periovulatory events and in vitro fertilization outcome is confounded by the fact that a periovulatory increase in prolactin with gonadotropin stimulation does not occur consistently in women and such rises have been asso-

ciated with a poor outcome in regard to successful pregnancy in in vitro fertilization cycles.

Nonetheless, the observations made by Dr. Dodds and his co-workers have made a valuable contribution to our understanding of the role of prolactin in the immediate postovulatory period. It will be of interest to learn of their proposed approach to elucidate further the preovulatory and postfertilization effects of elevated prolactin on oocytes and developing embryos.

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DR. MARTIN M. QUIGLEY, Cleveland, Ohio. Prolactin is a ubiquitous hormone with a multitude of effects on the reproductive system. The role of intrafollicular prolactin on subsequent fertilization in vitro, embryonic development, and subsequent pregnancy establishment is very much an open question. Some authors[1, 2] have reported increased rates of fertilization and pregnancy establishment in the presence of elevated intrafollicular prolactin. Others[3, 4] have reported decreasing follicular fluid levels of prolactin with increasing oocyte maturation and a better fertilization rate with lower levels of intrafollicular prolactin. Yet additional investigators[5, 6] have shown no relationship between follicular fluid prolactin levels and fertilization.

This study from The Ohio State University uses a mouse system to examine the effect of supplementation of the culture media with superphysiologic levels of prolactin on the success of in vitro fertilization and subsequent embryonic development in vitro. In addition, the effects of prolactin on the in vitro embryonic development of in vivo fertilized oocytes also are studied.

The authors' results are very similar to the prior publication of Fukuda et al.[7] In that study lower levels of prolactin (10 to 100 ng/ml) were used as culture supplementation, compared with the 150 to 600 ng/ml used in this study. The Fukuda study demonstrated that preincubating spermatozoa in culture media with elevated prolactin during their period of capacitation decreased, in a dose-dependent fashion, the fertilization rates. However, when spermatozoa were capacitated in prolactin-free media before being transferred into prolactin-supplemented media, the fertilization rates were uniformly slightly decreased in the prolactin-supplemented culture media, when compared with prolactin-free media. This effect was independent of the prolactin level in the media. A similar finding was not noted by Dr. Dodds and his associates. In both studies, however, subsequent embryonic development of oocytes fertilized in high-prolactin media, as well as the in vitro embryonic development of oocytes fertilized in vivo, was unaffected by the level of prolactin in the embryo growth culture media.

The real question, which neither the Fukuda study nor the present study was able to answer, is what effect elevated levels of prolactin during folliculogenesis and oocyte maturation have on subsequent fertilization and embryonic development. I believe this study demonstrates quite conclusively that elevated levels of prolactin have little, if any, impact on fertilization or postfertilization events. However, there remains the possibility that elevated prolactin levels in the culture media would adversely effect pregnancy establishment and outcome. A definitive answer to that question would require that the embryos exposed to elevated prolactin levels be transferred to pseudopregnant recipients and the pregnancy outcome monitored. However, that procedure is difficult and time consuming and the information gained probably would not be worth the investment in time and effort.

The question that really needs to be addressed is the role of elevated prolactin on oocyte maturation. A recent report[8] studied the effect of culture media supplementation with various protein and steroid hormones during oocyte maturation in vitro. These investigators demonstrated that the supplementation with prolactin (10 to 1000 ng/ml) enhanced, in a dose-dependent fashion, the subsequent embryonic development of these oocytes after fertilization in vitro. They postulated that both estradiol and prolactin played key roles in the promotion of preimplantational embryonic development.

The authors are to be congratulated for a well-designed and well-presented study. However, this investigation is but the first step in the clarification of the role of prolactin and fertilization.

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Dr. Robert W. Rebar, Cincinnati, Ohio. I wonder if I might just take a moment to speculate to or for Dr. Dodds and see what his reaction is. As Dr. Quigley noted, prolactin is a hormone that has been in search of a function for many years. More than a hundred functions have been ascribed to this hormone, and clearly we don't really know what it does under a lot of circumstances.

The one interesting observation that I think has been borne out is the fact that prolactin does alter glucose metabolism such that the response to glucose and the release of insulin are altered. I've always been amazed therefore that this particular field has not asked this question: Is there an indirect role for prolactin given the fact that we now know that insulin-like growth factor I receptors and insulin receptors play important roles within the follicle.

I have not seen any data addressing this particular question. Yet this might be one particular area of interest, particularly since there always has been the question about what prolactin could be doing during the follicular phase and particularly in the periovulatory phase of the cycle.

Dr. Dodds (Closing). First I would like to respond to Dr. Shepard's comment about the lack of oocyte retrieval from spontaneous cycling mice for an in vitro fertilization control. She is correct that mice in all of our experimental groups were stimulated with pregnant mare serum gonadotropin. We did not run a nonstimulated control; however, within our laboratory we have found no difference in the pregnant mare serum gonadotropin and natural cycle group with respect to fertilization and embryo development success. Pregnant mare serum gonadotropin stimulation simply increases the oocyte yield per mouse put to death.

In response to Dr. Quigley's comments, I agree that clinical studies that have tried to examine the relationship between prolactin and oocyte fertilization and embryo development are conflicting. His reference to the recent article from Dr. Wallach's group by Dr. Yoshimura concerning the effect of prolactin and estrogen on in vitro oocyte maturation brings up several important points. As Dr. Quigley has mentioned, Yoshimura has reported that the addition of prolactin and estrogen to in vitro oocyte maturation media did nothing to fertilization success; however, subsequent morula and blastocyst development was greatly increased. It is important to note that Dr. Wallach's group focused on gonadotropin, estradiol, and prolactin effects on in vitro maturation of immature oocytes and their subsequent fertilization and development. In contrast, we collected mature oocytes and studied the effect of prolactin on the fertilization and preimplantation embryo development. The results of the two studies are not contradictory. I think our study documents prolactin's lack of effect on mature oocyte fertilization and subsequent development while Yoshimura's study indicates prolactin is important in in vitro oocyte maturation.

The thing I found most interesting about Dr. Yoshimura's article was, as Dr. Quigley has mentioned, prolactin's improvement of morula and blastocyst transformation only when estrogen supplementation also was present. The unresolved problem that I have is that the studies by Channing and Nolin indicate that prolactin stimulates oocyte maturation inhibiting factor. In particular Channing has shown that prolactin stimulates porcine granulosa cell release of oocyte maturation inhibiting factor. In addition, Nolin reported homology between Channing's oocyte maturation inhibiting factor and prolactin. From this work, Nolin postulated that oocyte maturation inhibiting factor may be just an oligopeptide fragment of the prolactin molecule. In other words prolactin may be the parent molecule of oocyte maturation inhibiting factor. If prolactin does increase oocyte maturation inhibitor, it remains to be explained how prolactin functions in vitro apparently to improve oocyte maturation and subsequent preimplantation embryo development.

I agree with Dr. Quigley's comments that the role of prolactin in oocyte maturation will require further clarification. An in vivo model to address this issue would be optimum. In terms of Dr. Rebar's comment, I agree that prolactin may affect glucose metabolism; however, I do not know of any studies that have addressed that issue in the oocyte. It would be an interesting area to explore.

Another area that we are interested in is prolactin's potential role in stimulating lymphocytes. Prolactin may be important in stimulating endometrial lymphocytes that help the endometrium to become prepared to allow implantation. The effect prolactin may have on the endometrium represents just another, still ill-defined potential role that prolactin plays in the reproductive process.

The prevalence of substance abuse in patients with suspected preterm labor

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Premature labor is a recognized complication of substance abuse in pregnancy. However, the prevalence of substance abuse in patients first seen with symptoms of preterm labor and who deny use of illicit drugs is unknown. Between July 1, 1988, and December 15, 1988, 141 patients first seen at Northwestern Memorial Hospital in suspected preterm labor and a comparison group of 108 uncomplicated laboring term patients had urine toxicology screening performed to detect substance abuse. Positive urine toxicology screenings were found in 24 of 141 (17.0%) patients with suspected preterm labor and in 3 of 108 (2.8%) patients in the comparison group. The most common substance identified was cocaine (14/24 and 1/3, respectively). Of those patients in suspected preterm labor, 22 of 86 (25.6%) clinic patients had positive urine toxicology screenings as did 2 of 55 (3.6%) private patients. On the basis of our observations, we recommend that patients admitted in possible preterm labor be encouraged to submit to screening for substance abuse so that appropriate counseling and prenatal and neonatal care become available for these high-risk patients. (Am J Obstet Gynecol 1990;162:1562-7.)

Key words: Premature labor, substance abuse, cocaine

The neonatal complications of prematurity are responsible for the majority of adverse perinatal outcomes. Fuchs[1] reported that 8% of preterm births accounted for 75% of perinatal deaths, and it has been estimated that up to three fourths of mental and physical handicaps are directly linked to preterm birth.[2] Despite the aggressive use of tocolytic agents over the past decade, the incidence of preterm delivery has not decreased but remains at 7% to 10%.[3-5] Furthermore, whereas programs aimed at preterm birth prevention such as those advocated by Papiernik[6] and Creasy[7] have been reported to be beneficial, experience with such programs has not been uniformly successful.

Substance abuse is a recognized risk factor for preterm delivery.[5, 9] However, the prevalence of substance abuse in patients first seen with symptoms of preterm labor and who deny substance abuse is unknown. The present study was undertaken to determine the magnitude of this problem at our institution, a tertiary center within a large urban area.

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Material and methods

The study population comprised 141 patients first seen at Northwestern Memorial Hospital between July 1, 1988, and December 15, 1988, in suspected preterm labor (between 22 and 36 weeks' gestation). Patients were excluded if they admitted to substance abuse during the current pregnancy or if they were taking prescription medication that might lead to a falsely positive urine toxicology screening. As part of our routine evaluation of patients suspected to be in preterm labor, a urine specimen was analyzed for the presence of illicit drugs (e.g., marijuana, cocaine, benzodiazepines, opiates, barbiturates, amphetamines, methadone hydrochloride, and phencyclidine hydrochloride) shortly after admission. Positive screens did not affect obstetric decisions on labor and delivery but prompted referral to our comprehensive perinatal clinic for women with substance abuse.[10]

To determine the prevalence of undetected substance abuse in our term population, 108 arbitrarily chosen patients with uncomplicated pregnancies at ≥37 weeks' gestation similarly had urine screenings obtained when in early labor and analyzed for the presence of illicit drugs. These screenings were performed on otherwise discarded urine specimens and testing was performed at no cost to the patient. Demographic data were collected without identifying information so that patient anonymity and confidentiality were maintained.

Patients first seen with regular uterine contractions suggestive of premature labor were initially managed

Table I. Demographic data

	Suspected preterm labor (n = 141)				*Term labor*			
	Clinic (n = 86)		*Private (n = 55)*		*Clinic (n = 39)*		*Private (n = 69)*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Maternal age	23.6 ± 5.2	—	30.7 ± 5.8	—	25.1 ± 5.0	—	31.6 ± 5.0	—
Primigravid	19	22	16	29	± 9	23	25	36
Patients with ≥ one living child	53	62	19	35	23	59	30	43
Employed	11	13	39	71	11	28	54	78
Married	8	9	47	85	12	31	63	91
Race								
White	16	19	42	76	2	5	60	87
Nonwhite	70	81	13	24	37	95	9	13

with bed rest and intravenous hydration. Those patients with intact membranes whose contractions ceased were discharged and their activities were restricted. Tocolysis with intravenous magnesium sulfate or ritodrine was initiated in patients with persistent regular uterine contractions at gestational ages of <36 weeks; observation of documented cervical change was encouraged but not required for the diagnosis of preterm labor. Patients with suspected preterm labor complicated by premature rupture of membranes were managed expectantly without an attempt at tocolytic therapy. Hospitalized patients and those discharged with oral β-sympathomimetic agents prescribed underwent follow-up with weekly nonstress tests and serial ultrasonographic examinations for fetal growth. Oral β-sympathomimetic agents were continued until 37 weeks' gestation or until labor ensued.

Statistical analysis of the prevalence of substance abuse and outcome measures was performed with the Student *t* test, the Fisher exact test, and the χ^2 test where appropriate. Significance was assumed at the $p < 0.05$ level.

Results

Demographic data for both the preterm and the term patients are listed in Table I. The results of urine toxicology screenings for both patient groups are shown in Table II. Positive screenings for use of illicit drugs were noted in 24 of 141 (17.0%) preterm and 3 of 108 (2.8%) term patients ($\chi^2 = 12.83$; $p < 0.001$). The most commonly identified substance was cocaine, (14/24 and 1/3, respectively). More than one illicit drug was identified in six patients.

Of those patients in suspected preterm labor, 22 of 86 (25.6%) clinic patients had positive urine toxicology screenings compared with 2 of 55 (3.6%) private patients ($\chi^2 = 9.94$; $p < 0.001$). Six of 58 (10.3%) white patients had positive urine toxicology screenings compared with 18 of 83 (21.7%) nonwhite patients (p, NS).

Table II. Urine toxicology results

	Suspected preterm labor (n = 141)	*Term labor (n = 108)*
Positive screening		
Cocaine	14	1
Cannabinoids	9	1
Opiates	2	0
Other (barbiturates, benzodiazepines, phencyclidine, amphetamines)	6	1
No. of patients with positive screening	24 (17%)*	3 (2.8%)

*More than one illicit drug was identified in six patients.

The demographic distribution of the term comparison group is representative of the obstetric patient population at Northwestern Memorial Hospital. The three (7.7%) positive urine toxicology screenings were identified in the 39 clinic patients; there were no positive urine toxicology screenings in the 69 private patients.

Outcome measures are depicted for the preterm study group in Table III. Within the clinic and private patient subgroups, the identification of illicit drug use was not associated with differences in the mean or distribution of gestational age at delivery, mean birth weight, or incidence of a small-for-gestational-age newborn.[11] There were also no differences in the use of tocolytic drugs or the incidence of premature rupture of membranes.

Comment

The incidence of illicit drug use in our population of patients first seen with symptoms suggestive of preterm labor but who previously did not admit to substance abuse during the index pregnancy was 17% (24/141). This problem was not limited by demo-

Table III. Outcome measures in suspected preterm labor subgroups

	Clinic (n = 86)		*Private (n = 55)*	
	Positive toxicology (n = 22)	*Negative toxicology (n = 64)*	*Positive toxicology (n = 2)*	*Negative toxicology (n = 53)*
Gestational age at screening (wk)	31.8 ± 3.9	30.6 ± 3.8	29.5 ± 9.2	30.8 ± 36
Tocolytic therapy	5 (23%)	7 (11%)	0	14 (26%)
Premature rupture of membranes	4 (18%)	22 (34%)	1 (50%)	15 (28%)
Gestational age at delivery (wk)	35.8 ± 3.1	34.0 ± 4.7	38.5 ± 3.5	36.6 ± 4.2
Delivery				
≤32 wk	5 (23%)	19 (30%)	0	9 (17%)
<37 wk	15 (68%)	45 (70%)	0	26 (49%)
Birth weight (gm)	2508 ± 726	2405 ± 976	2753 ± 809	2677 ± 953
Birth weight <10th percentile	2 (9%)	4 (6%)	1 (50%)	5 (9%)

graphic boundaries, although urine toxicology screenings were more often positive in clinic patients than in private patients.

The most common substance identified was cocaine, which has been reported to have a strong association with preterm birth, placental abruption, growth retardation, and possibly with congenital anomalies.[9, 10, 12, 13] Cocaine has a sympathomimetic effect by blocking the reuptake of norepinephrine and dopamine from the postsynaptic neuron. The resultant increased availability of neurotransmitters produces an abrupt peripheral vasoconstriction, tachycardia, and hypertension.[14] In addition, parenterally administered cocaine in the pregnant ewe has been shown to reduce uterine blood flow and increase uterine contractions.[15] Although some investigators have found marijuana to be more commonly abused by pregnant women than cocaine, our data are in keeping with a recent 36-hospital survey. In that report 0.4% to 27% had screenings positive for substance abuse with seven hospitals reporting cocaine abuse in >9%.[16]

Somewhat surprising to us was the observation that patients with positive urine toxicology screenings were subsequently delivered of infants with similar gestational ages and similar birth weights compared with those with negative screenings. We cannot be certain as to the extent identification of use of illicit drugs influenced ultimate outcome but this knowledge may contribute significantly. Indeed, multidisciplinary nonjudgmental interventions aimed at abstinence for the remainder of pregnancy have been shown to improve perinatal outcome.[9, 10]

The 2.8% (3/108) incidence of substance abuse in our comparison group is consistent with reports that suggest use in 1% to 10% of the pregnant population.[16-18] Our frequency of positive intrapartum urine screenings could be construed as low for an urban population, but substance abuse is sporadic and a single negative urine toxicology study underestimates use over an entire pregnancy. It is difficult to obtain an ideal comparison group for patients in suspected preterm labor, and the demographic characteristics of our two groups differ. This likely reflects the known association of prematurity with nonwhite race and low socioeconomic status—factors that may also be associated with the prevalence of the use of illicit drugs.

Although our study does not show a cause-and-effect relationship, we found a high rate of positive urine toxicology screenings in women admitted in suspected preterm labor. Most risk factors associated with premature delivery cannot be altered, but substance abuse is potentially treatable. On the basis of our observations, we recommend that patients admitted with symptoms suggestive of preterm labor be encouraged to submit to screening for substance abuse so that appropriate counseling and prenatal and neonatal care become available for these high-risk patients.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. ROBERT J. SOKOL, Detroit, Michigan. In this study, Dr. Ney and her colleagues found that positive urine toxicologic screenings for drugs of abuse were sixfold more common in patients without previously known substance abuse who were first seen in suspected preterm labor than in those first seen in labor at term. On this basis, they recommend urine toxicologic screening of preterm labor patients. The most common drug identified was cocaine. Cocaine use in pregnancy has been reported to be associated with increases in spontaneous abortion, stillbirth, low birth weight (both preterm delivery and intrauterine growth retardation), premature rupture of the membranes, abruptio placentae, neonatal behavioral change and possibly congenital anomalies including those of the eyes, skeletal system, and urinary tract.[1] Clearly, the authors have hit on an important subject on which to focus attention.

Although I believe that the observation made by the investigators is sound, there are questions concerning both the methods used in this study and the inferences made from it. First, how were the groups chosen? There is nothing to indicate that the preterm patients studied were a consecutive series or how the control group was actually selected other than the statement that it was arbitrary. Could there be selection bias?

On the basis of the increase in cocaine use detected in patients entering the hospital with symptoms of preterm labor, the authors speculate on a possible physiologic mechanism. Because some risks associated with preterm labor are also associated with cocaine use (e.g., low socioeconomic status and premature rupture of the membranes) their argument could be considerably strengthened by a multivariate analysis to adjust for confounding; unfortunately they did not perform one.

To attempt to isolate any impact of cocaine on preterm labor, we submitted data from a sample of 3316 consecutive patients who entered a prospective study of perinatal drug and alcohol abuse to discriminant analysis. We contrasted preterm births with nonpreterm births for maternal characteristics, cigarette smoking, and drug and alcohol abuse. In light of types of substance use in isolation, preterm delivery was associated with heavier smoking, higher alcohol intake, and greater likelihood of cocaine and opiate abuse, as in the study under discussion. However, when the risks are considered jointly the only significant difference in substance use between our groups was that the mothers who were delivered of preterm infants were more likely to use narcotics. There was no difference in cocaine use. This does not support the investigators' speculation that pharmacologically linked cocaine and threatened preterm labor. However, the authors evaluated drug use just before admission, whereas in the Detroit data, drug use was documented throughout pregnancy but not specifically on admission for labor. Thus, cocaine use might act as an acute trigger for uterine contractions—the multivariate analysis presented here does not rule out this possibility, but the small series presented by the authors does not have adequate power to detect differences that might support the possibility. Further studies in human pregnancy are needed.

Finally, what about the authors' recommendation for urine toxicology for patients first seen in preterm labor? To evaluate this recommendation one has to make some suppositions. Given that urine toxicologies for drugs of abuse could be obtained for $25 each, and given the prevalence of positive results in the study for staff patients of 26%, it would cost just <$100 to detect each substance abuser on a staff service. But among private patients with a much lower prevalence of substance abuse (<4%), the cost per ascertained case rises to almost $700. The situation is worsened by the insensitivity of a single urine screening.[2] It is likely to miss perhaps one half to two thirds of patients who abuse drugs. Also, detection when the patient is already in premature labor is too late to prevent most of the adverse perinatal consequences of cocaine. Detection early in pregnancy could facilitate focussed prevention. Thus, a more cost-effective approach might be to begin screening early in pregnancy, but only for populations with a high prevalence of substance abuse or possibly for patients who have other factors associated with substance abuse, such as low socioeconomic status or cigarette smoking.[3] I would be interested in the authors' views on this approach.

Even with the caveats raised in these comments, I reemphasize the importance of this finding. In a series of >3000 patients so far unreported from our service at Hutzel Hospital in Detroit, Dr. Enrique Ostrea, chief of Neonatology, has performed toxicologic screenings on meconium—a method at least two to three times more sensitive than isolated urine screenings in the detection of perinatal substance abuse. A total of 42% of all deliveries showed at least one drug; 20% of the meconium samples showed evidence of cocaine use during pregnancy (Enrique M. Ostrea, Jr., MD, personal communication). This is truly a problem of epidemic proportions, one of which as obstetricians we must be acutely aware.

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DR. VIRGINIA R. LUPO, Minneapolis, Minnesota. The problem of substance abuse in pregnancy is still taboo in many prenatal clinics and labor and delivery suites throughout the country. Physicians trained more than 3 or 4 years ago have probably never managed a patient with a crack-induced abruption or seen a child with a porencephalic cyst as a result of an anoxic cerebral intrauterine insult. The relationship of cocaine to precipitate delivery at any gestational age was only described in 1983 by David Acker at Boston City Hospital,[1] and even now the contribution of this drug to preterm labor and delivery is not acknowledged in the day-to-day workings of many obstetricians. The thought "my patient cannot have this problem" still prevails. The importance of Dr. Ney's study lies in confronting us with the prevalence of drug abuse among women in preterm labor in a mixed public-private suburban hospital and compels us to look for similar substance abuse among our own patients.

I do have several questions about this well-designed and much needed study.

Did your institutional review board require informed patient consent before participation in this study? If so, did some potential study participants refuse and do you think this in any way biased your results such that an underreporting of substance abuse occurred?

Was the widespread use of cocaine relative to the cannabinoids expected? Did any pattern of combined substance abuse arise? I am constantly surprised by the varying patterns of substance abuse observed throughout the country. Because the excretion of cannabinoids can last up to 2 to 3 weeks, the 6% prevalence reflects the use in the past several weeks before admission. However, the cocaine assay reflects drug use only in the past 48 hours because of the rapid metabolism of this compound. In some respects the cannabinoid assay could be said to detect prevalence and the cocaine assay could be said to detect incidence. It is somewhat unusual to see more use of cocaine than of cannabinoids in the general population. Recently I completed a survey of patients at nine different labor and delivery suites in the Minneapolis—St. Paul area, searching for use of controlled substances among 1800 women. I realize that the inclusion of opiates and barbiturates can be confusing in statistical results, inasmuch as many of these drugs may be used on a prescription basis. Even if cocaine and cannabinoid use only was reported in Dr. Ney's study though, a prevalence of 16% of urine tests would be seen. In my study, cannabinoid use exceeded cocaine use in the public, private, and mixed public-private hospital.

I am curious as to whether a pattern was seen in which cocaine was selectively associated with cannabinoid use, or did cannabinoids function as a marker for abuse of other substances?

Does the subset of preterm labor patients who use cocaine deliver earlier than the nonusing population? The observation that women with positive drug screens were delivered of infants no earlier on average than women with negative screenings leads me to question the subcategories of specific drug use. Because we have little reason to suspect cannabinoid use as a cause of preterm labor and delivery, I am curious as to whether the cocaine-abusing patients were delivered of infants earlier than women negative for substance abuse.

Finally I would like to comment on the issue of drug screening in pregnancy. Cocaine is a large cause of preventable abnormal neonatal outcome. The ability of this drug to destroy family integrity because of drug-seeking behavior is a national tragedy. In Minnesota we have a law that mandates any physician who suspects a pregnant women of drug abuse to perform a urine toxicology screening and if results are positive the physician is mandated to report this to the local child protection services, which consider such use as neglect. Provision for the implementation of civil commitment proceedings for drug treatment is also present within this law. Our state has several residential drug treatment centers tailored to the needs of pregnant women, and some provide for these women to keep their other children with them while in treatment. The physicians of our state strongly believe that this law will help protect the mose defenseless new members of our society while not criminalizing the behavior of their mothers. The law may dissuade some women from seeking prenatal care but it is a much more sympathetic approach than that currently debated in the California legislature, which proposes mandatory 3-year imprisonment for women found to be abusing drugs during pregnancy.

Substance abuse, especially cocaine abuse but also abuse of legal drugs such as alcohol and nicotine, is a problem that will not go away by ignoring it. If it has

not spread to every private, every rural, and every hometown hospital in this country, wait a couple of weeks; it is coming. Studies such as Dr. Ney's underscore its extent. It is for us as physicians to be right out in front as the media and the legislatures try to assess, judge, and punish the users. Our first and only mission as physicians is to heal. This must be done by relentless diagnosis of the disease of drug abuse, by treatment of the disease, and by protection of the children from the rampages of the disease.

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DR. ROBERT GOODLIN, Denver, Colorado. In the Denver General Hospital the use of cocaine appears to have increased roughly 300% to 400% in the past few years, but our incidence of premature labor has actually gone down.

DR. EDUARD EICHNER, Cleveland, Ohio. I just want to go back a few generations. Back in the late 1920s and early 1930s we used cocaine to stop nausea and vomiting in pregnancy. We did not get toxicity, and we stopped it soon enough; the patients cooperated with us actually. There was no problem there. That was at the time when cocaine had become a local anesthetic for tonsillectomies.

At about the same time, The Upjohn Company took morphine out of their cough syrup because of the drug law and replaced it with heroin. Within a couple years we were involved with marked toxicity and heroin drug habit formation, so much so that in the middle 1930s Upjohn took heroin out and replaced it with codeine.

The only other thing along that same line is the start of prohibition at the time. We as physicians were given permission to write alcohol prescriptions for our patients if we deemed it necessary. Unfortunately, we never got the data as to whether it was good, bad, or indifferent; but I thought I would let you know.

DR. NEY (Closing). I will comment first about the possible selection bias of our study groups. We attempted to screen sequential patients first seen with symptoms of preterm labor. Patients who were first seen on the labor and delivery suite with contractions at <37 weeks' gestation were screened per protocol. These patients were not necessarily delivered of preterm infants but did come to the hospital with contractions. It is true that you do not always screen every patient who meets criteria, but we did make that attempt. As for our term group, we also attempted to get sequential patients during a 2-month period.

We were looking not only at the prevalence of unsuspected substance abuse, but also at whether there is a link between substance abuse and preterm contractions before preterm delivery. Our belief is that once preterm delivery occurs, it is too late. We wanted to determine whether we could effect a decrease in premature delivery in detection of abuse and referral of these patients to special intervention programs.

I agree with Dr. Sokol that we need to do further study and that we did not distinguish the contributions of cigarettes and alcohol in these subgroups.

I appreciate Dr. Sokol's cost analysis. He clearly shows benefit for our clinic population. I do not think that $700 is too much to pay to detect a substance abusing private patient who is in premature labor, who has not yet been delivered of infants, and whose pregnancy outcome we may improve.

In reference to Dr. Lupo's comment about patient consent and the possible loss of some patients, in Illinois, Minnesota, and quite a few other states when a urine toxicology is indicated as part of a medical evaluation, patient consent is not required. Our patients were informed that the urine toxicology was to be done as part of our evaluation of preterm labor, but consent was not solicited.

Dr. Lupo has found, as have other researchers in this field, that marijuana, not cocaine, is the most common drug of abuse. I think this reflects our study design. We excluded patients who admitted to drug abuse during the index pregnancy because our purpose was to detect the rate of unsuspected substance abuse. Marijuana may be a more common admitted drug of abuse in the general population. Because our entrance criterion was suspected premature labor and cocaine has been implicated to cause uterine contractions, we may have selected for cocaine. I agree that we have not shown cocaine to be more common than marijuana, simply that it appeared more often in this study because of the reasons stated.

We are asked by Dr. Lupo to reanalyze our data and separate cocaine from other substances of abuse. The small numbers involved preclude meaningful conclusions with the data so divided, but I agree that a larger series should be so analyzed. For purposes of description, of the 14 patients who tested positive for cocaine with preterm contractions, 10 (71%) were delivered of infants at <37 weeks' gestation; of the 10 patients who abused only substances other than cocaine, 5 (50%) were delivered of preterm infants; and 71 of the 117 (61%) patients with negative urine screenings were delivered of preterm infants.

Selective termination: Clinical experience and residual risks

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Assisted reproductive technologies have aided thousands of couples, but complications have resulted in multifetal pregnancies creating a bitter irony for infertility patients. In an effort to increase the rate of intact survival, we have successfully performed transabdominal first-trimester selective termination procedures on 22 pregnancies including one octuplet, five quintuplet, twelve quadruplet, and four triplet gestations. There have been eight sets of twins, and two singletons delivered, seven twin pregnancies are ongoing, and one early and four late losses of pregnancies. With experience we now counsel as to a high likelihood of a technically successful procedure, but we still have concerns for late losses. We have tried to balance the arguments about the direct harms of performing selective termination and the obstetric risks of not performing selective termination. We believe that selective termination should not be considered a "social" procedure. Our data do not yet make clear whether one, two, or three is the optimal number of embryos to leave. Therefore, on the basis of both current obstetric risk factors and ethical reasoning we will continue to support our protocol of optimally leaving twins. (Am J Obstet Gynecol 1990;162:1568-75.)

Key words: Selective termination, multifetal pregnancy, fertility drugs

Multiple gestation is a high-risk situation associated with marked increases in maternal complications, perinatal mortality, and morbidity.[1] These risks appear directly proportional to the number of fetuses. The average length of gestation has been estimated to be 35 weeks for twins, 33 weeks for triplets, and 29 weeks for quadruplets.[2] The spontaneous occurrence of multiple pregnancy with three or more fetuses is unavoidable and rare, (1:8100 births for triplets, 1:729,000 births for quadruplets). It is a more frequent sequelae of ovulation induction or in association with assisted reproduction technologies such as gamete intrafallopian transfer (GIFT) or in vitro fertilization (IVF). The incidence of multiple gestation after ovulation induction ranges from 6% to 8% with clomiphene citrate to 15% to 53% with gonadotropins.[3]

Although advances in prenatal care and intensive neonatal care have reduced the mortality and, to a lesser extent, the morbidity of prematurity, the obstetric outcome for triplets or higher number of fetuses is significantly worse than for singleton or even twin pregnancies.[4, 5] The ability to carry quadruplets or more is by any reasonable definition, significantly compromised.

Complications from the use of powerful fertility drugs such as human menopausal gonadotropin (Pergonal preparation of menotropins) or newer agents such as urofollitropin (Metrodin, follicle stimulating hormone preparation) have thus created one of the ultimate ironies in medical care. Usually reserved as the last resort for couples with very significant infertility problems, the use of such drugs has led to situations in which previously infertile women may bear more fetuses than they can safely carry to viability. Spectacular reports both in the medical literature and in the lay media have detailed successes such as the Dionne quintuplets of the 1930s, but also equally infamous tragedies such as the Frustaci septuplets of California in 1985. Whereas the successes have touched the public's heart, the reality is the tragedy of prematurity with associated high risk of fetal death, and significant impairments for survivors have more generally been the rule.[4]

When faced with such potentially tragic circumstances, couples have had to choose among several unpleasant options. Termination of the entire pregnancy with the intent to conceive again is one option. However, because most of these patients are treated for infertility and another conception is not guaranteed, this option has generally been considered unacceptable. A second option is to continue with all the fetuses. In cases of quadruplets or even quintuplets, survival of some or all is certainly possible, but there is significant risk of long-term morbidity. With six or more fetuses

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the chance of survival is extremely low, and in the case of octuplets, the chance is essentially zero.

A third option is selective termination, which over the course of the past few years has become an accepted option when faced with the potential perinatal tragedy associated with multiple fetuses.[6-9] We report here our experiences with 22 such procedures over a 3-year period, from both the scientific perspective and the ethical and public debates that have evolved.

Material and methods

During a 3-year period (January 1986 through April 1989) we counseled 25 couples who had multifetal pregnancies as a result of treatment of infertility. Of 22 couples who came to our program for counseling and selective termination, three were from the Detroit metropolitan area; the remainder were referred from many areas of the country. Of these 22 couples, 17 had no children, three had one child, one had two children, and one had three children. Twelve pregnancies had been achieved through gonadotropin induction, six through GIFT, and four through IVF.

The approach to counseling for selective termination has continually evolved over the 3-year period. Originally our counseling emphasized the dearth of reliable information about the outcome of multifetal pregnancies, recognized that most reports in the lay media were heavily biased toward either spectacular successes or tragedies, and was particularly deficient with regard to information on early pregnancy losses. Further, we knew that much of the available data were anecdotal. Initially we also did not know what the chances would be of successfully performing the procedure. We did not know what the risk of long-term complications might be during both the remainder of the pregnancy and postnatally. We emphasized that the procedure could result in the loss of the entire pregnancy and that the exact risks were unknown. Our present counseling has evolved to include an essentially 100% chance of technically performing the procedure, but continues to stress the uncertainty as to long-term complications and potential risks from the procedure.

For selective termination we used ultrasonographic equipment (GE3600, General Electric, Denver) equipped with a 3.5 and 5.0 MHz linear array transducer. A "free hand" technique of needle guidance was used in all cases.

For the first two patients, one woman with quadruplets and one with octuplets, the procedures were performed transabdominally by repeated needle punctures of the embryonic thorax to produce mechanical disruption of the fetus. All the remaining cases have been done by intrathoracic injection with a 22 gauge needle of approximately 0.5 ml of potassium chloride solution (2 mEq/ml) (Fig. 1). The duration of the procedure per embryo has varied from 3 minutes to 1 hour. Because we learned that a sharp angling of the needle through the skin is more painful to the mother than a direct, downward, vertical approach, in nearly all cases a separate transabdominal needle entry has been made for each embryo.

Results

In five of the 22 patients, the number of embryos we found on ultrasonography was different from expectations on the basis of the presenting history. In three patients we found fewer and in two others we found more than the number expected.

In 21 of the 22 pregnancies, with our encouragement the couples elected to reduce the number to twins, regardless of the starting number of fetuses (Table I). One woman with quadruplets wished to be reduced only to triplets. One woman asked to go to a singleton pregnancy. However, we believed we could not fulfill that request; we have detailed our ethical reasoning previously.[6]

All 22 attempted procedures were performed successfully, reducing the number of embryos to the desired number. All were done at one sitting except for the octuplet pregnancy that was deliberately performed in two sessions separated by 1 week. The majority of the procedures were done at 10 or 11 weeks' gestation (Table II).

Five patients lost the entire pregnancy after selective termination. Approximately 1 week after an apparently uneventful procedure, one woman suffered a spontaneous abortion of the remaining two embryos. Four other women lost their twins later in gestation (Table II). Of these, in one case one of the remaining twins had Potter sequence, although scans at 1 and 3 weeks after the procedure had been normal. She suffered rupture of membranes at 20 weeks' gestation and lost the twins. In a second case, rupture of membranes followed genetic amniocentesis performed by a highly qualified physician. In the remaining cases premature labor and spontaneous rupture of membranes occurred, respectively. In two other patients one of the remaining twins was lost—one at 1 week after the procedure and the other after a genetic amniocentesis. Normal singleton pregnancies continued. Fifteen twin pregnancies have been delivered—13 at >35 weeks' gestation, one at 28 weeks' gestation, one at 31 weeks' gestation, and two singletons near term. All have been appropriate for gestational age with no obvious congenital abnormalities.

Comment

Clinical issues. Our experiences over the past 3 years and those of a few other groups around the world[7-13] have shown that selective termination can be success-

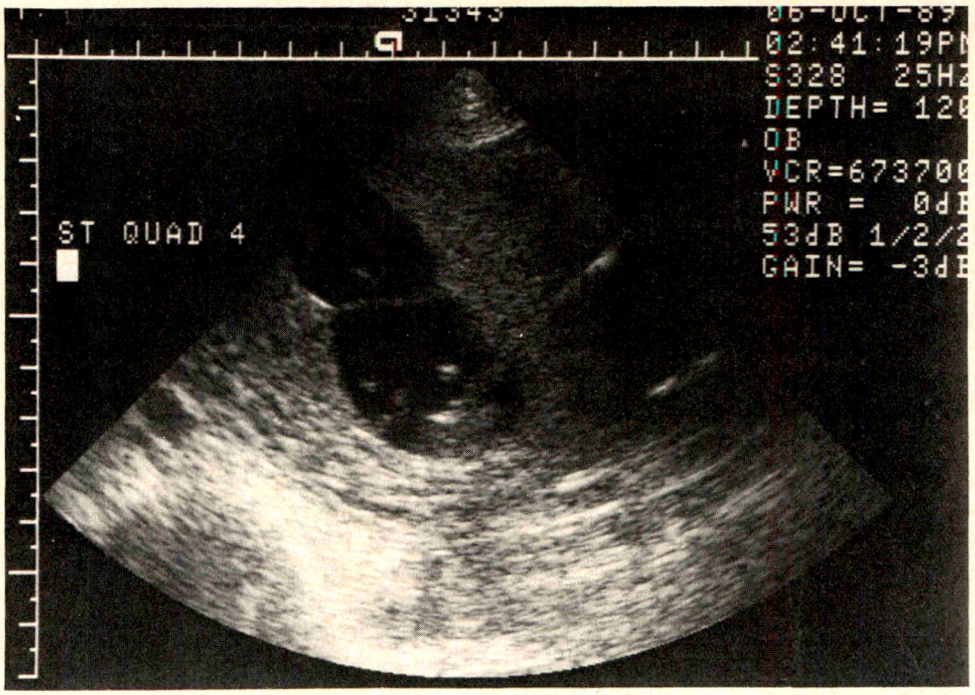


Fig. 1. Ultrasonically guided entry of 22 gauge needle into embryonic thorax.

fully accomplished, and for the majority of patients live born twins will be born. Our pregnancy loss rate (5/22 or 22.7%) is lower than the 35.4% (4/11) reported by Berkowitz et al.[7] and higher than the 11.9% (5/42) reported by Salat-Baroux et al.[10] However, Salat-Baroux mentions only immediate complications (post-procedure infections) leading to pregnancy loss. Immediate pregnancy losses (within 1 week after the procedure) occurred in one case each in ours and in Berkowitz's[7] series and were associated with vaginal bleeding. Late rupture of membranes was not reported in Salat-Baroux's study,[10] but has affected patients in both Berkowitz's and our series. Dumez and Oury[8] originally used a transcervical suction method, but abandoned it after experiencing an approximately 40% loss rate. We have concerns that the transcervical aspiration of the lower sacs in the uterus, as used by Salat-Baroux,[10] may cause devitalization of the membranes over the internal os. Such devitalization could create a potential nidus for ascending infection that may predispose the patient to premature membrane rupture several weeks later.[7] However, we have seen ruptured membranes even when the transabdominal approach was used exclusively and the lower gestational sacs were avoided.

Questions remain concerning the risk/benefit ratio of selective termination and are based in part on the fact that information on the natural history of multifetal pregnancies is still very incomplete. We have collected such data and have found that there are considerable discrepancies between the experiences reported by perinatologists, who often deal with what we believe is a biased sample, as compared with those reported by reproductive endocrinologists, who can more fully document early fetal loss.

The best time to perform the procedure is in part dependent on the method used to achieve reduction of fetal number. Advocates of the transcervical or transvaginal suction approach generally tend to perform the procedure earlier, between 6 to 9 weeks' gestation. In our patients, with the use of a transabdominal approach most procedures were done at 10 to 11 weeks' gestation. Although performance of the procedure as early as 6 to 7 weeks' gestation is feasible, at this age there still seems to be a considerable risk for the spontaneous loss of embryos. For example, with ultrasonographic documentation of viable twins in early pregnancy, a 21.2% incidence of "vanishing twins" has been reported.[14] Three of our patients had spontaneous loss of fetal heart activity between initial diagnosis and procedure (generally a 3 to 5 week period), although we cannot exclude simple misdiagnosis of fetal number. If the procedure is done relatively early in gestation (before 8 gestational weeks), there would still be concern about the possibility of ending up without viable fetuses even when one or two were intentionally left intact. With the transabdominal approach, procedures at 9 to 11 weeks' gestation have seemed technically easier and our original concerns[6] about disseminated intravascular coagulation (as related to a larger mass of fetal tissue left

in utero) have not been borne out. Thus, we recommend a transabdominal approach at 9 to 11 weeks' gestation for selective termination procedures.

We have suggested, for both clinical and ethical reasons that reduction of the number of fetuses to twins was most appropriate. Further clinical evaluation of our data will be required before the optimal number of living embryos, whether it be one, two, or three can be determined. Because selective termination is not a "social" procedure and on the basis of our belief that there is currently no medical or ethical justification for reduction to fewer than twins, we have turned down requests to reduce one normal twin or to reduce triplets or more to a singleton pregnancy. The obstetric complications and outcome of twins are somewhat worse than that of singleton pregnancies.[1-3] However, twins leave some margin for error in the event something happens to one of the remaining twins as has been seen in our series. Furthermore, these patients are essentially all infertility couples for whom two children may satisfy their family planning desires. The reported lower loss rate by Salat-Baroux[10] may be a function of both lower average starting numbers and perhaps lower stopping number. The issue of whether there is better perinatal outcome of singletons versus twins will require a much larger data set and must be factored by the starting number and other confounding variables.

With the current protocol there continues to be a high loss rate. To date it is not clear how to interpret the data as to which cases may have been procedure related, the technical issues of a learning curve, and whether overall better perinatal outcome might not be achieved by aiming for singleton pregnancies. If so, we will have to rethink out ethical arguments.

Ethical and political issues. We have previously reported in great detail an ethical justification for our first attempts to offer selective termination and for choosing *selective termination* as the term for this procedure.[6] Public opinion and the media in general have accepted the concept that the first-trimester embryo is not yet a viable person and therefore is endowed less protection under the law than that of a child. This allows the concept of selective termination to remain within the realm of ethical standards acceptable to the general populous, whereas the concept of selective infanticide would never be considered acceptable within the same standards.

Whereas we have not been surprised by the negative response of antiabortion groups, we have been pleased by the general acceptance of the view that the ethics of selective termination are very different from the ethics of abortion per se. Despite the inherent controversy that surrounds any technology that involves abortion, we have received only one "hate" letter written in crayon and have had begrudging acceptance even from very conservative quarters. One of us (M. I. E.) has been attacked by the editor of a support group for triplets who declared in the *Triplet Connection* that she was "horrified recently to learn of a fertility specialist in Detroit who performs selective abortions on all patients with more than two infants" demonstrating clearly that they had not read our original article.[6] None of us is an endocrinologist, nor do we do infertility work. The *Triplet Connection* contends that the outcomes in multifetal pregnancies are good and therefore selective termination should hardly ever be needed, and if done should reduce the number of embryos to three or even four. Our survey of their data is less optimistic than their conclusion. However, we certainly agree that everyone's data are significantly flawed, and all interpretations are tenuous.

The introduction of techniques such as embryo cryopreservation may help to reduce the risk of multifetal pregnancy associated with replacement of multiple embryos in IVF or GIFT. It seems that the relatively few cases of multifetal pregnancies that result from treatment, despite the approximately 20,000 patients per year in this country who are treated with gonadotropins, must be considered a major success rather than a tragedy. We believe that selective termination is a small price to pay for the thousands of babies made possible for childless couples. However, we do believe that selective termination should not be viewed as an end, but only as an interim step until improvements in infertility treatment alleviate the need for its use.

Table I. Selective termination procedures

No. of pregnancies	*First seen with*	*Reduced to*
1	Octuplets	Twins
5	Quintuplets	Twins
12	Quadruplets	11 twins, 1 triplet
4	Triplets	Twins

Table II. Timing and outcome of selective termination

Gestation (wk)	8	9	10	11	12
No. of procedures	1	2	12	6	1
Pregnancy losses	0	0	2*	3†	0

*Case 3, one fetus with Potter sequence, spontaneous rupture of membranes at 20 weeks' gestation. Case 4, premature onset of labor at 18 weeks' gestation.

†Case 9, spontaneous rupture of membranes after genetic amniocentesis at 17 weeks' gestation. Case 10, vaginal bleeding for 1 week with subsequent loss at 12 weeks' gestation. Case 15, spontaneous rupture of membranes 7 weeks after procedure.

In summary, we believe that selective termination has been shown to be a contribution in the treatment of the tragic circumstances of a multifetal pregnancy. However, we do not yet have the data base to know definitely at what number of embryos selective termination should first be offered or what number of embryos should optimally be left. Until better data are available we will continue the current protocol on the basis of our present experience of offering selective termination to multiple gestations of three or more with reduction of embryo number to twins.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Marilynn C. Frederiksen, Chicago, Illinois. Dr. Mark Evans and his colleagues have presented their clinical experience in the performance of selective fetal termination in patients with multiple-gestation pregnancies as a result of ovulation induction. In their previous article they took the position on a principled ethical basis that they could not support the performance of selective fetal termination for purely social reasons.[1] However, with the use of a utilitarian (risk/benefit) argument they could justify selective termination in grand multiple-gestation pregnancies because without such a procedure all fetuses would be lost or suffer significant perinatal morbidity. They further argued, again with the use of a pure risk/benefit analysis, that reduction of fetal number to twins was optimal. This in essence is the hypothesis that this second article is testing. They report from their experience that selective termination is technically feasible. They report an overall pregnancy loss rate of 22.7%, of which only a small portion (1 loss from 22 procedures) can be procedurally related. It remains to be proved whether the remaining pregnancy losses are procedurally related or related to the decision to reduce these multiple-gestation pregnancies to no lower than twin gestations.

Of comparative interest Salat-Baroux et al.[2] described in a 1988 article a somewhat different transcervical procedure to reduce multiple-gestation pregnancies. His clinical series reported the pregnancy outcome of 42 multiple-gestation pregnancies that were selectively reduced. The overall pregnancy loss rate was only 11%, thought to be directly related to the procedure. In the remaining 37 pregnancies, selective reduction resulted in 62% singleton gestations and 38% twin gestations with no reported late losses. His procedure and subsequent pregnancy management cannot be directly compared with that described by Dr. Evans and most probably has a a higher procedurally related pregnancy loss rate, 5 of 42 versus 1 of 22, respectively. However, his clinical protocol allowed for the majority of patients to carry singleton gestations, and perhaps this accounts for the pregnancy loss rate that was half that reported by Dr. Evans.

To assess the fetal loss rate of singleton versus twin pregnancies, we analyzed 6 years of data, comprising some 25,700 births that occurred at ≥20 weeks' gestation, from Memorial Hospital of Northwestern University and found a greater than fourfold higher loss rate in pregnancies with twin gestations as compared with singleton gestations. This should remind us and serve to emphasize that a singleton pregnancy is less likely to result in fetal mortality.

Dr. Evans bases his clinical protocol of reducing multiple gestations to twins on a risk/benefit analysis, but the data presented do not answer whether leaving a twin gestation provides a better outcome than a singleton gestation. If Dr. Evans and his colleagues wish to decrease the overall residual risk, and indeed increase the number of women who take well babies home, then his clinical protocol needs to show that reduction to a

twin gestation offers less risk and more benefit than reduction to a singleton gestation.

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Dr. Frank H. Boehm, Nashville, Tennessee. The article by Dr. Evans and his colleagues contains important information for those of us who administer health care to women because of several factors. First, the 22-patient sample size provides considerable experience and information that can be used in counseling patients who are candidates for such a procedure. Second, the ethical discussion, whereas controversial, does stimulate the thinking process on this contemporary issue.

The problem of multifetal pregnancy is not rare. Anovulation and ovulatory disorders are present in approximately 20% of infertile couples, and ovulation is achievable in >90% of these women with approximately 1% to 2% resulting in a greater number of conceptuses than twins.[1] Thus many of us will face the problem of properly counseling patients at some stage on the subject of selective termination.

Evans and his group have presented 22 patients who underwent selective termination. These patients had several initial options including aborting all pregnancies, which would result in no live births. At the other extreme, among the 22 patients there were 93 potential live births if intervention was refused after the patients were told of a multifetal pregnancy. With today's technology in perinatal and neonatal medicine, however, these two extremes seem less than ideal. With the assumption that selective termination is not offered, we know that morbidity and mortality of multifetal pregnancies is considerable. Even in the more hopeful situation of triplet gestation, a recent review of 238 cases revealed a 20.3% perinatal mortality rate and a high morbidity rate.[2] Another option that would not involve selective termination involves offering and performing abortion on the six patients with quintuplets and octuplets. This would have resulted in 60 potential live births among the 22 patients. Abortion could of course be offered to the 18 women with quadruplets or more, resulting in only 12 potential live births.

However, if selective termination is offered, as was the case in this report, the number of potential births depends on the number of fetuses left intact. Termination to a singleton gestation would result in 22 potential live births, whereas termination to twins in this group of 22 patients would result in 44 potential live births and termination to triplets would result in 66 potential live births. By promoting termination to twin gestation, Evans and his colleagues achieved 32 potential live births and lost a total of 12 fetuses in 7 patients.

Therefore, we must ask ourselves which of the options are we most comfortable with, and which of the options do we present to our patients? I maintain that all options should be offered to our patients, and that we do so before the process of ovulation induction. It is only in this pretreatment phase that a couple can be properly counseled as to the options they face, and may decide not to attempt medical induction of ovulation because of the potential ethical concerns and dilemmas should a multifetal pregnancy occur. An American College of Obstetricians and Gynecologists' publication[1] states that the process of ovulation should be explained to patients and that potential complications and risks for both mother and fetus, as well as the chances of success, should be outlined. Although not specifically mentioned, selective termination, because it involves abortion, should be discussed in the preovulation induction counseling session. Waiting until a multifetal pregnancy has already occurred in a patient who has strong feelings against abortion and then sustains a poor outcome could result in a charge of wrongful life or birth.

The authors state that they do not know at what number of embryos selective termination should be offered or what number of embryos should optimally be left. I do not believe this is the physician's decision. It is the patient who must decide after having been told the necessary facts and risks for both multifetal pregnancies and selective termination. If physicians have trouble deciding what to offer patients because of the complexities and variables, is it any wonder that our patients may be troubled?

With this article and several others in the literature we are beginning to develop a data base by which to properly counsel our patients. However, this counseling should take place before induction of ovulation so that those patients who do present themselves as candidates for selective termination will have had optimal time to thoroughly discuss and contemplate the several options that are available to them.

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Dr. Maurice J. Mueller, Crescent Springs, Kentucky. Dr. Evans has recently proposed the establishment of an international registry of these multiple pregnancies, and I believe this will give us the information to more effectively counsel these patients.

The review article that Dr. Boehm mentioned was in August 1989 *Obstetrical and Gynecological Survey* by Petrikovsky and Vintzileos. They classified these multiple pregnancies of high fetal order into different numeric classifications such as triplets and quadruplets. The article of Petrikovsky and Vintzileos can be used in coun-

seling patients. There are support groups that can help these parents; in California there is the Triplet Connection and New Jersey has Mothers of Multiples. These can be used for preconceptual counseling.

Dr. Robert M. Rebar, Cincinnati, Ohio. I feel compelled to make a couple of comments. I think everyone in the room would agree that Dr. Evans and the discussants raised important issues in this matter. Clearly we are at a window in time when we have the opportunity to offer our patients technologic advances that do not always result in optimal outcomes. I think the most important statement that Dr. Evans may have made was that selective termination should not be viewed as an end but rather should be reviewed as something that is with us for the present and hopefully will change in the future.

I should think that with the advances in reproductive medicine there will come a time when we will talk about frozen oocytes and frozen embryos and be done with the problems that result from these multiple pregnancies.

In addition, it is interesting to me that in the use of menopausal gonadotropins personally for >15 years, we have not yet achieved anything more than a twin gestation; and that is even before the use of the ultrasonographic technologies that now exist. I think we have known for many years that the use of human menopausal gonadotropin in women who ovulate normally has a clearly increased propensity to result in multiple ovulations and lead to these tragic outcomes that involve more than triplet gestations. I think that the reason we are seeing an increase in some of these multiple gestations derives from the inappropriate use of these agents in a number of cases.

To be sure, we will see these multiple pregnancies in some of the newer technologic procedures such as IVf and GIFT, but there really should not be any reason to see more than three fetuses when human menopausal gonadotropins are used.

I was surprised that Dr. Evans did not discuss the psychologic impact of the procedure on the patients involved. I have been involved with multiple pregnancies that resulted from GIFT with only one couple who considered this alternative. Watching that couple wrestle with the possible choices even with assistance was clearly a very enlightening experience for me and a difficult experience for them.

Last, I think that the statements made by Dr. Boehm are also quite important: that is, to discuss the risks of therapy before the institution of ovulation induction. However, I would remind everyone in this room—and we all are aware of it—that how we present the risks and the benefits of a given procedure clearly also determines the choices that the patients make in our offices. It is possible for different physicians to present the same data to the same patients and have the patients arrive at different decisions merely on the basis of the way of the data are presented to them.

These are difficult issues. They are not issues that will be resolved here, and they are certainly ones that merit our discussion as well as discussions by lay persons.

Dr. Robert J. Blaskiewicz, St. Louis, Missouri. I have two questions for Dr. Evans. One is, who did the counseling? The second is, what is the perinatal mortality rate at your institution for quadruplets and triplets.

Dr. Evans (Closing). From Dr. Frederiksen's remarks, we completely agree that the choice of stopping at twins initially was made on the basis of a utilitarian approach in large measure. I think one fundamental concept that we all have to recognize is that ethics do evolve with technology. I think it is possible that as the perinatal morbidity and mortality of triplets gets better over the next 10 to 15 years, that the point at which the risk/benefit ratio to most people seems to be acceptable might move up. Some people may think it is one now. Some people may think it is two. Some people now also think it is three or even four. I think you may see the number move up as the outcome of triplets and quadruplets improves.

Since these 22 cases were reported, in the past 6 months we have actually performed the procedure for another 14 cases, of which we have had only one loss early in pregnancy and one loss later, suggesting to some degree that the twins outcome may be somewhat better.

As Dr. Mueller said, I am putting together an international registry in which we now have a couple of hundred cases from around the world. I think we are finding that there is still a lot of debate among most centers as to whether one or two is the optimal number of fetuses at this point.

I do agree completely with Dr. Boehm that these issues ought to be discussed preconceptually. Of course, I think it is also quite clear that many patients do not want to hear this kind of information and it does not register even if you spend a lot of time discussing it with them. That is something that needs to be seriously addressed.

It is very clear, as I think we all understand, that some of the cases we have seen should never have happened and probably with better management would not have happened. I think it is also clear that the best infertility specialists with the best of equipment and best of intentions will have this kind of problem occasionally occur. One other philosophic benefit we have seen from our infertility colleagues is there are some patients who are very resistant to gonadotropins. The knowledge that selective termination exists may allow them to be more aggressive in the management of an individual patient, which may mean the difference between getting her to ovulate and to not ovulate. However, the window for getting one or possibly two eggs to ovulate may be very narrow, and there may be a significant overshoot.

I do not have the data to prove it, but I do believe in terms of the specific risks once you have done the procedure are proportional to the starting number.

The study that Dr. Frederiksen mentioned of Salat-Baroux et al. had a higher percentage who started with triplets than we did. To answer Dr. Blaskiewicz's question, of the patients we have counseled, I have counseled all of these patients myself.

We have had essentially none with quadruplets refuse the procedure. We have had about 50% of the patients I have seen with triplets decide to proceed with triplets. This is somewhat biased. Of the now three dozen patients for whom I have performed the procedure, only a few of them have actually come from Michigan. So with the majority of the patients, we have had discussions on the telephone before they fly in to have further in-depth counseling followed by the procedure.

That also obviates the question about what are the perinatal mortality and risks of delivery in our center because of the 36 patients, only one of them has actually had her obstetric care and delivery at Hutzel Hospital. That was a set of quintuplets down to twins, both of whom have done well.

I think, in a pluralistic society, we have to offer our patients all options. However, I think we have to step back from it a little to avoid the issue of merely being technicians to our patients' desires. Whereas some have said that if you are willing to do an abortion of a singleton pregnancy, why would you not be willing to do two to one? I think the issues are very different. Whereas I do not think doing two to one should be made illegal or abortion for sex selection, as has been suggested, should be made illegal, I think that in my personal views that would be unethical. That crosses the line between doing a procedure for a medical indication versus one for a social indication, and I believe I have the right to decline to be involved with that; but I also believe the patient should have the option to pursue that someplace else if so desired.

Although it was not mentioned, I think we have also seen criticisms about how this procedure can be abused such as in sex selection. For example, if a patient who has twins, one boy and one girl, decides she wants to only have a boy or only have a girl, that would be an abuse of the procedure. I have had a couple of patients call to request such and I have declined to be involved.

The data presented by Petrikovsky et al. are very enlightening. However, they still are relatively small. It is hoped that from the registry we are putting together we will be able to have better numbers in a year or so.

Dr. Rebar's comment about the psychologic impact on these patients is very important. All these patients go through a grieving process. The octuplet pregnancy was one of my first two patients for the procedure; and as with many medical procedures, they often start doing something new when you have nothing to lose. It was very clear for the patient with octuplets that there was essentially a zero chance of any survival, let alone with significant morbidity and mortality with an octuplet pregnancy. So that actually made the situation for her relatively easy to reach a conclusion. But still she did wrestle with the loss of the potential other children she might have had. This couple and essentially all the other couples I have seen have felt that this was either the only way or by and large the best way in which they could go home with happy, healthy children.

As far as the support groups, the Triplet Connection for example, what we have found is that if you ever want to see biased counseling, that is where you get it. The Triplet Connection with which I have more experience has lambasted me as the fertility expert in Detroit who aborts all his multiple pregnancies. They never bothered to either call me or even read the article. A, I am not an infertility specialist; and B, that is exactly the opposite of what we have said. They do have a biased population; but even if you take a random sample of one of their publications, it is full of "Our condolences to Mrs. Jones, our condolences to Mrs. Smith."

If you add their own morbidity and mortality, I think it comes out with triplets at around the 20% level that was alluded to early on. I believe that with quadruplets probably the chance of at least one of them having a significant problem is >40%, and it is >50% certainly with quintuplets.

I think the most important point we can have, as Dr. Rebar said, is we must not look at selective termination as an end but only a short-term solution until the point at which our fertility treatments will not give us more embryos than can be safely managed during pregnancy.

Spontaneous cell death in the chorion laeve

Tim H. Parmley, MD

Little Rock, Arkansas

The granulosa cells of the dominant follicle grow, differentiate, and die in a roughly predictable amount of time. Because the simultaneous death of this population of cells results in menstruation, one may say that the life span of this population of cells "times" the menstrual cycle. Metamorphosis in amphibians and morphogenesis in several vertebrates are other examples of developmental milestones that are "timed" by the life span of specific cell populations. In all these examples, cell death is associated with a specific histology, apoptosis. Apoptosis characterizes the cell death that produces the progressive disappearance of the trophoblast in the chorion laeve as term is approached. Therefore, the histology of trophoblastic death in the near-term chorion laeve corresponds to that of populations of cells with life spans that "time" developmental events. The trophoblastic cell population of the chorion laeve is prematurely destroyed by infiltrating maternal leukocytes in cases of chorioamnionitis. (Am J Obstet Gynecol 1990;162:1576-83.)

Key words: Chorion laeve, apoptosis, labor, chorioamnionitis

Individual cells go through cycles in which they are created by division of a precursor, grow and differentiate, and then eventually die. When large numbers of cells do this in a synchronized manner, the result may be the acute loss of an entire tissue. The corpus luteum is an example of such a collection of cells that grow, differentiate, and die in a synchronized manner.[1] Because the simultaneous death of all the hormone-producing cells in the corpus luteum results in menstruation, the life span of the cells of the corpus luteum may be said to measure the length in time of the luteal phase. The timing of many developmental phenomena is apparently controlled by similar collections of cells that synchronously live and die. The timing of some morphogenetic events in vertebrate embryos is achieved in this manner.[2-4] Metamorphosis in amphibians and in insects is similarly "timed."[5, 6]

In each of these examples the life span of the synchronized cells may be prolonged or shortened by other factors such as disease and endogenous hormones. When this alteration occurs the developmental event timed by the life span of the cells is hastened or delayed. An example is that human chorionic gonadotropin (hCG) may prolong the life span of the cells of the corpus luteum and delay endometrial breakdown. For this reason, the synchronized death of the cells is not a primary cause of the developmental event (i.e., morphogenesis, metamorphosis, or menstruation) but only a part of the mechanism that times them. Other factors that control the life span of the cells are more properly termed *primary causes*.

When cell death occurs, in each of these instances it takes the distinctive form of apoptosis. Apoptosis, as opposed to necrosis, is an active energy-requiring process in which single cells die and are removed by phagocytosis without producing an inflammatory reaction.[2] Apoptosis characterizes not only the spontaneous cell death associated with the developmental events mentioned above but many others as well. It appears to be the mechanism of spontaneous cell death in terminally differentiated cells. Glucocorticoids induce differentiation in many cell populations and this may be the mechanism whereby they produce apoptosis.[7] Apoptosis also characterizes tissues that involute when hormone support is withdrawn,[8] such as premenstrual endometrium. Histologically, apoptosis is characterized by condensation, shrinkage, and ultimate fragmentation of nuclei. Cytoplasmic shrinkage and destruction occurs simultaneously, resulting in highly eosinophilic bodies that often contain nuclear fragments. The bodies seem to pull away or shrink from neighboring cells.

Inasmuch as gestation is a reproductive event with a finite length, we asked if a population of synchronized cells could be located with an apparent life span correlated with the length of gestation and with a mode of death characterized by apoptosis. The increasing interest in the fetal membranes as the site at which labor is initiated suggested that such a population might be found in the amnion or chorion laeve.

Material and methods

We selected a 6-month period over which it was institutional policy to send all placentas for pathologic examination. We then reviewed the clinical records from each case in which a placenta had been submitted. A case was selected for study if the clinical estimate of

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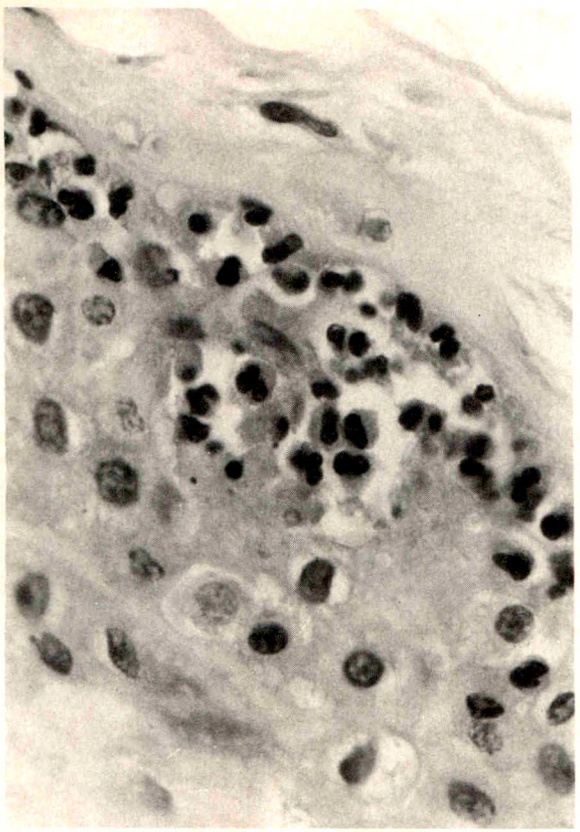


Fig. 1. Maternal leukocytes are collecting in trophoblastic cell layer of chorion. There is already significant destruction of much of this cell layer. However, none of infiltrate has progressed into mesodermal connective tissue of chorion, which lies above. Trophoblastic cell layer is about six cell layers thick, which is characteristic of late second trimester or early third trimester chorion. Maternal decidua lies below.

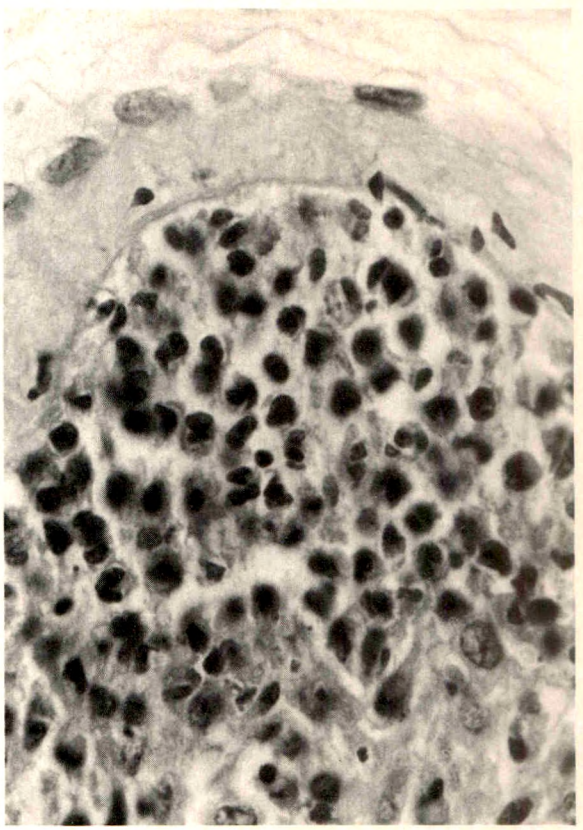


Fig. 2. Although trophoblastic cell layer of chorion has been destroyed there is still no infiltrate in connective tissue above trophoblastic cell layer. Amnion is out of illustration above.

gestational age agreed with that predicted by the stated last menstrual period, at least one antepartum ultrasonographic estimate, and the delivered infant. Gestational age was rounded to the nearest even-numbered week. The histologic slides were then examined by light microscopy with particular attention given to the trophoblastic cell layer of the chorion. As the material had not been collected prospectively or quantitatively it was possible only to estimate the amount of any given histologic feature. However, placentas had been processed by a modification of the method suggested by Benirschke and Driscoll[9]; therefore in each case there was a section of rolled fetal membrane on file. We also examined the remnants of the cytotrophoblastic shell in the decidua beneath the placenta proper. This material was more fragmentary.

Results

Table I lists the amount of material obtained at each gestational age. The 121 cases were clinically heterogeneous. Elective cesarean deliveries and cases complicated by maternal diabetes or toxemia were included. However, with the exception of abruptio placentae and chorioamnionitis, no associated clinical condition produced any apparent difference in the histology of the membranes other than that difference attributable to gestational age alone. This difference is described below.

A total of 18 cases from pregnancies terminated between 18 and 26 weeks' gestation all showed histologic chorioamnionitis. The trophoblastic cell layer was the first fetal layer to be infiltrated by maternal leukocytes (Fig. 1). The leukocytes accumulate in this layer before they move into the overlying mesoderm. Their presence was associated with near destruction of this layer, so that by the time they moved into the overlying mesoderm the trophoblast cell layer was gone (Fig. 2). Subsequently they tended to form in another layer immediately beneath the compact zone that supports the amnion. Then microabscess formation occurred followed by destruction and loss of the overlying amniotic epithelium. In the one case of abruptio placentae seen in this gestational age group, blood dissected between the maternal decidua and the trophoblast.

As expected,[9] the incidence of chorioamnionitis fell after 26 weeks' gestation. From a total of 29 cases dated from 28 through 32 weeks' gestation, 14 (50%) showed

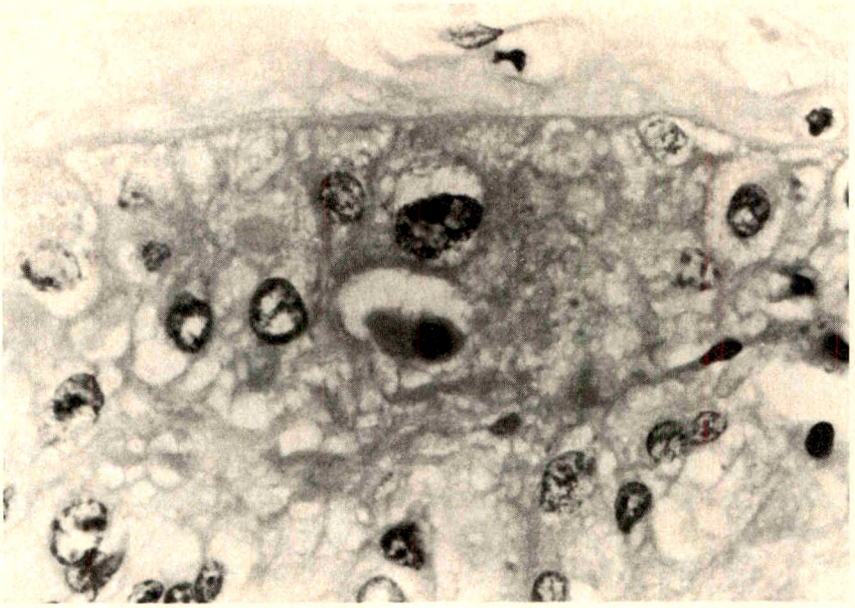


Fig. 3. One cell with dark shrunken nucleus and eosinophilic shrunken cytoplasm around it lies in middle of illustration. It appears to have withdrawn from normal tissue around it. Just above this cell, another cell may be beginning very early apoptosis as indicated by some nuclear condensation. This example of trophoblastic cell layer is about four or five cell layers thick. Although this feature is variable and may be affected by angle of section, it is fairly typical of membranes from early to middle third trimester.

chorioamnionitis. As described above, the trophoblastic cell layer was infiltrated and destroyed early in the process. In the 15 cases without chorioamnionitis, scattered individual cells within the trophoblastic cell layer exhibited the characteristic histology of apoptosis or spontaneous cell death. There was no associated inflammatory reaction. Described in detail by Searle et al.,[2] apoptosis consists of the shrinkage of both nucleus and cytoplasm. The nucleus becomes condensed and dark and eventually fragments (Fig. 3). The cytoplasm becomes highly eosinophilic and may be irregularly contracted so that cytoplasmic projections exist (Figs. 4, 5). The whole cell, now smaller, seems to shrink away from its neighbors, which are normal in appearance. Homogenous eosinophilic material, deposited focally in the cell layer where cell death had occurred, was similar in appearance to eosinophilic material deposited over placental trophoblast called the Nitabuch layer. This eosinophilic material tends to disappear as term is approached. In the two cases of abruptio placentae between 28 and 32 weeks' gestation, retroplacental blood had dissected into the space between the trophoblast and the decidua.

Of the 30 cases dated between 34 and 36 weeks' gestation, nine showed chorioamnionitis. In the rest, apoptosis was much more prevalent than in the 28- to 32-week material. By 36 weeks' gestation, there were foci where the trophoblastic cell layer was absent, and maternal decidua was directly opposed to fetal connective tissues (Fig. 6). Many of these sites lack even the eosinophilic material. In one case, there was a purely local, chronic inflammatory reaction that was quite dissimilar to the acute reaction observed in chorioamnionitis.

From 38 to 42 weeks' gestation there were 43 total cases. Two showed chorioamnionitis. The histology of one case of chorioamnionitis at 42 weeks' gestation was unusual in that the minimal inflammatory infiltrate did not initially concentrate in the trophoblastic cell layer, because this cell layer was absent. Apoptosis was widespread. The maternal decidua was in direct contact with fetal connective tissue at multiple sites.

At all gestational ages the delivered placentas possessed only fragments of the decidua basalis. Thus, thorough study of the fate of those trophoblastic cells that infiltrate the implantation site was not possible. However, our impression was that they share the same histologic fate as the trophoblastic cells in the chorion laeve.

In only one instance did the criteria outlined in our methods section convincingly suggest a 44-week pregnancy. The histology of the membranes was consistent with that view. There was relatively massive thinning of the trophoblastic cell layer. Maternal decidua and fetal connective tissue were in direct contact over broad

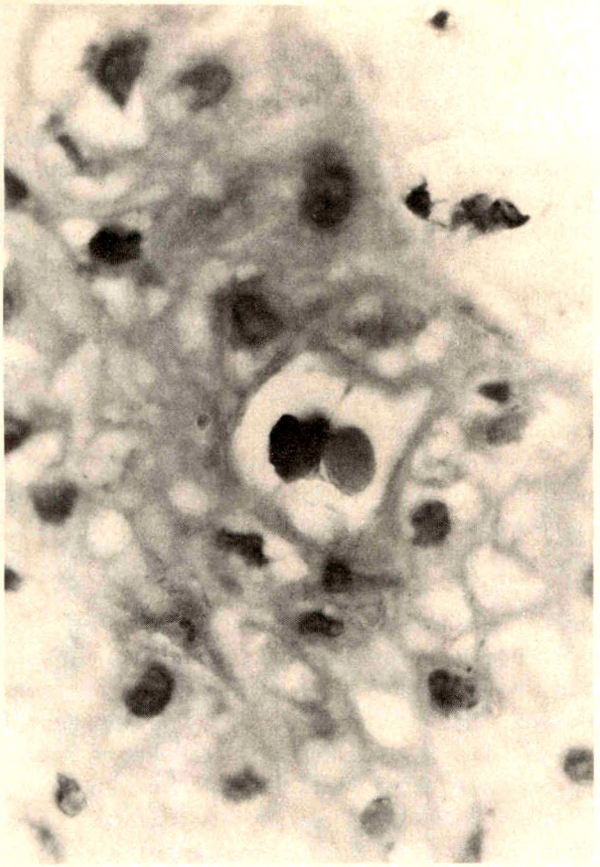


Fig. 4. Two apoptotic cells are seen in trophoblast. At right is eosinophilic cell body of one that has shrunken from the normal tissue around. At left, cytoplasm of second cell is not clearly discerned because of dark pyknotic nucleus.

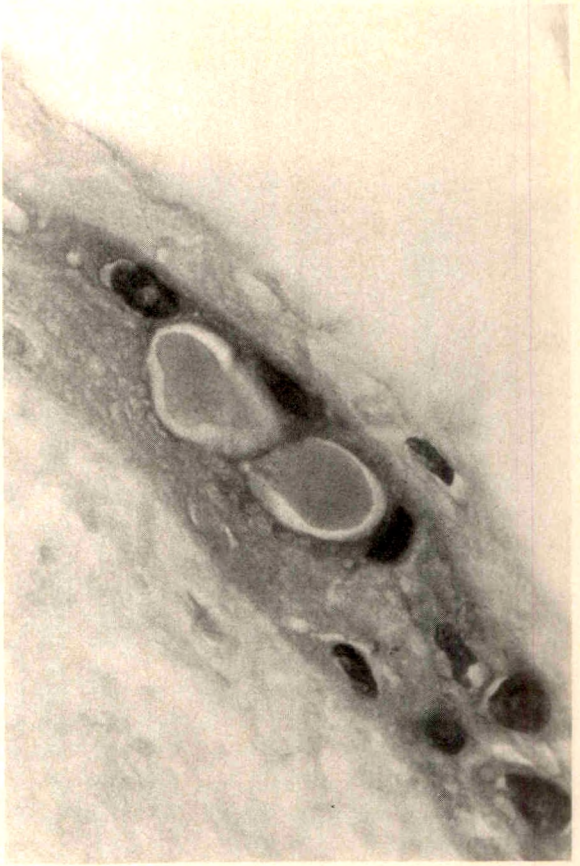


Fig. 5. Two cells have become apoptotic side by side. Nuclear fragments are not apparent in these cells and only their dense eosinophilic cytoplasm is seen shrinking from tissue around them. Early apoptotic changes in adjacent cells may be indicated by their increasingly dense nuclei. This example of trophoblast cell layer of chorion is about two or three cell layers thick, which is fairly characteristic of chorionic membranes from late third trimester.

areas. Extensive apoptosis characterized those sites of remaining trophoblast.

In summary, the trophoblastic cell layer of the chorion laeve had widespread apoptotic cell death and loss of the trophoblastic cell layer as term approached. In cases complicated by chorioamnionitis, the same tissue was prematurely destroyed by the maternal inflammatory infiltrate. This occurred very early in the course of the development of chorioamnionitis.

Comment

We have drawn two conclusions. The first is that trophoblast in the chorion laeve thins and progressively disappears as term is approached. Individual cell death, apoptosis, is a prominent histologic feature of this process. The fact that apoptosis characterizes this process is a new observation but the fact that the trophoblast in the chorion laeve disappears in a patchy manner as term nears is not new. In 1962 Bourne[10] described the histology of the chorioamnion in detail. Most of his material was obtained from deliveries that occurred at term and his description is of term membranes. However, he did have enough preterm material to recognize that some of the observations he made on term membranes represented changes that occurred as term approached. An example was what he called "degenerative changes" in the trophoblastic cell layer of the chorion. The cells of this layer were replaced by "granular, fibrin-like material." These were "diffusely scattered as irregular plaques" over term membranes. He believed that they were often associated with necrosis of the underlying decidua.

The second conclusion is that the trophoblastic cell layer of the chorion laeve is destroyed very early in the course of chorioamnionitis by the maternal inflammatory infiltrate. Although this observation is not new,

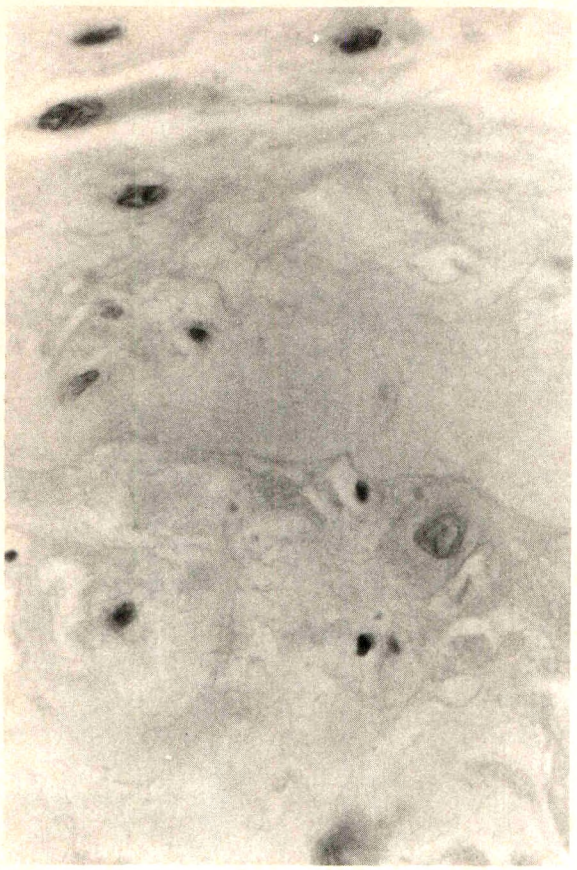


Fig. 6. Above lies mesodermal connective tissue of chorion. Amnion is out of illustration above. Below is maternal decidua, which lies immediately adjacent to connective tissue of chorion with no intervening trophoblast. One degenerating cell may represent remnants of trophoblastic cell layer.

Table I. Placentas examined

Gestational age (wk)	*No. of cases*	*Abruptio placentae*	*Chorioamnionitis*	*Frequency of apoptosis*
18	1	—	1	Obscured by chorioamnionitis
20	2	—	2	—
22	4	—	4	—
24	3	—	3	—
26	8	1	8	—
28	7	1	3	+
30	6	—	3	+
32	16	1	8	+
34	14	—	5	+ + +
36	16	—	4	+ + +
38	19	—	1	+ + + +
40	13	—	—	+ + + +
42	11	—	1	+ + + +
44	1	—	—	+ + + +

little emphasis has been given to how early in the course of the inflammatory process the trophoblastic cell layer may be destroyed.

More speculatively, if it is suggested that the life span of the trophoblastic cell layer of the chorion laeve, under physiologic or some pathologic conditions, measures the length of gestation, then this view is consistent with much of the current thinking about the onset of parturition.[11] Rising amniotic fluid levels of glucocorticoids after 30 weeks' gestation might induce apoptosis in the chorion laeve.[12] Glucocorticoids are known to induce apoptosis,[7] and prednisolone produces premature trophoblastic death in the placenta of rodents.[13] Moreover, anencephaly, a condition associated with prolonged gestation, results in the biologic opposite of apoptosis. The trophoblast in the body of the placenta of an anencephalic fetus fails to morphologically mature in human beings.[14]

The loss of the trophoblast in the chorion laeve would be expected to result in a local decrease in anything the trophoblast produces, including progesterone.[15] It also might include a decrease in the ability to metabolize any locally produced prostaglandin.[16, 17] Further, if amniotic fluid factors are important in the initiation of labor then the loss of a tissue between the amniotic fluid and the maternal decidua might result in increased transfer of the amniotic fluid factors to the maternal tissues.[11] The gradual rather than acute loss of the trophoblastic cell layer would be consistent with the inability (to date) to show any dramatic changes in hormone physiology immediately before the onset of parturition.

In the case of chorioamnionitis, if the life span of the trophoblastic cell layer of the chorion laeve measures the length of gestation then the premature destruction of the trophoblastic cell layer by maternal leukocytes would result in premature labor. This destruction might occur either because of the initiation of the physiologic mechanism suggested above or in response to other components of the inflammatory reaction released incidental to the maternal leukocytic infiltration, such as cytokines or prostaglandins.[18] The very early and nonspecific nature of this event would be consistent with the high but less than universal correlation of premature labor, histologic chorioamnionitis, and documented infection.[19, 20]

In any case the widespread loss of the trophoblastic cell layer in a 44-week pregnancy and the presence of relatively large amounts of trophoblast in some cases of premature labor is strong evidence that the relationship of the life span of this tissue to the length of gestation is not a simple one. Furthermore, if the life span of the extraplacental trophoblast is important in timing the length of gestation, then the trophoblast that infiltrates the decidua basalis and has not been studied cannot be ignored.

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Discussion

Dr. Daniel K. Roberts, Wichita, Kansas. The author's demonstration that trophoblastic epithelium of the chorion laeve disappears as gestational term approaches is not new information. However, it is new information that the process responsible for this phenomenon is apoptosis. This is important because it suggests that the tissue loss is a physiologic process rather than nonspecific degeneration. The process of an orderly maintenance and termination of gestation is the most likely explanation.

The author further shows that the maternal inflammatory infiltrate associated with chorioamnionitis destroys the same tissue layer that spontaneously disappears as term nears. This destruction takes place very early in the course of the development of chorioamnionitis. If the trophoblast of the chorion laeve is responsible for the maintenance of gestation, then its destruction by maternal leukocytes would promote the termination of gestation, and thus provide a link between chorioamnionitis and premature delivery.

The author appropriately points out that some of his observations are inconsistent with his hypothesis. Some examples of prematurely delivered placentas without chorioamnionitis still have much of their trophoblastic tissue. In another case, labor had not begun until 44 weeks' gestation despite extensive loss of the trophoblastic layer. These cases could be explained by individual variation or by unknown pathophysiology. I would like the author to comment further on this.

The speculation that apoptosis is the mechanism that controls gestational termination provides the principal interest in this article, but as the author correctly points out, only morphologic conclusions can be reached from morphologic studies. I look forward to the experimental studies that might confirm or refute this possibility. These might include comparative studies with other animals in addition to more quantitative studies. Ultrastructural evaluation might also be interesting.

In addition to the comment with regard to discrepant findings, I would like to ask the author:

1. You indicate that in apoptosis "other factors" rather than inherent timing are the primary causes. Please explain further.

2. If apoptosis is the manner of destruction in premenstrual endometrium, why are neutrophils present during that phase?

3. If apoptosis is a time-mitigated response, how might it play a role in the aging process?

4. What role do you believe this mechanism plays in the initiation of labor?

Dr. Michael W. Varner, Salt Lake City, Utah. Professional communications in clinical medicine can vary from case reports, through retrospective or prospective series, to prospective, randomized trials. All these formats have been of value in obstetrics and gynecology. However, all these formats also have potential hazards that must be considered before their conclusions can be accepted.

This study is a retrospective series describing histologic changes in chorioamnionic membranes. As with any retrospective study, questions must be routinely asked about patient selection criteria, operational definitions, associated complications and conditions, and

potential unavailability of confirmatory evaluations and laboratory or research tests.

A total of 121 patients of clinically certain gestational age were included in this report. They were collected during a 6-month interval when all placentas were routinely submitted for pathologic evaluation. This strikes me as a small number for a university referral service and I wonder whether any statistical calculations were undertaken to address the question of adequate sampling.

The major dependent histologic variables are the progressive decline in histologic chorioamnionitis and increase in apoptosis with progressive gestational age. Whereas associations seem to be present, I always worry when cases are evaluated in a nonblinded fashion and would suggest that these findings be confirmed in a prospective, blinded study.

In the manuscript, chorioamnionitis is only defined in histologic terms. I wonder how chorioamnionitis is clinically defined on the author's service and what proportion of patients had this clinical condition? The manuscript states that the histologic changes occurred early in the course of the development of chorioamnionitis and I wonder how closely the clinical diagnosis correlated with the histologic diagnosis?

Any information about associated complications and conditions would be both informative and potentially suggestive of coexistent explanations or causes. Elective cesarean deliveries were included. Does the absence of labor affect the frequency or intensity of the histologic findings? Did any of the patients receive antenatal steroids? I wonder what proportion of women, particularly in the preterm group, had premature rupture of the membranes?

In addition, were any of the pregnancies associated with other conditions, such as fetal asphyxia, that might predispose them to leukocytic infiltration?

A final hazard of any retrospective series is the potential subsequent unavailability of confirmatory evaluations and laboratory or research tests. What proportion of these women had cultures performed of their amniotic fluid, chorioamnionic membranes, placentas, uteri, or newborns? In the absence of confirmatory cultures the diagnosis of chorioamnionitis must be considered questionable.

It would also be interesting to correlate these changes with presumptive biochemical markers of labor such as prostaglandin metabolites. Romero and associates[1] have shown that prostaglandin E_2, prostaglandin $F_{2\alpha}$, and their respective metabolites are elevated in the amniotic fluid of women with intraamniotic infection and preterm labor. In the absence of intraamniotic infection, the elevation in premature labor is modest. In the future it might also be interesting to correlate these findings with endogenous host-response products to presumed infection such as tumor necrosis factor or interleukin-1.

I would like to address a subpopulation of this study that I think is of particular importance and significance, namely, those patients between 26 and 32 weeks' gestation. Before 26 weeks' gestation, neonatal outcome is usually bad and beyond 32 weeks it is usually good. A total of 50% of patients in this intermediate group had histologic chorioamnionitis. I wonder whether these histologic findings correlate with perinatal parameters such as clinical asphyxia or respiratory distress syndrome. If they do we might be able to develop a screening or predictive test that could identify premature labor patients at highest risk for suboptimum outcomes.

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Dr. L. Russell Malinak, Houston, Texas. In a majority of the slides without chorioamnionitis, there was a single cell or only two cells with this change. What is the fate of the healthy looking cells, and are they candidates for this same process? If so, why did we not see histologic evidence of that process in more cells?

Dr. Edgar L. Makowski, Denver, Colorado. Dr. Parmley, were the membranes that were examined consistently obtained from the same location? Second, the slides that you projected with destruction of the trophoblastic cells appear rather avascular. As a result, do you see any evidence of destruction of the accompanying vascular bed? This would be of great clinical significance because there would be a decrease in the density of the vascular bed and it could affect the transport of nutrients and respiratory gases.

Dr. Dinesh M. Shah, Nashville, Tennessee. In the presentation by Dr. Parmley, there is an inherent assumption that the mechanism for maintenance of gestation resides in the existence of the trophoblastic cells in the chorion laeve. The current overwhelming endocrine evidence would suggest that it probably resides in the placenta. In the same light, I have a question. If the primary contribution of chorion laeve at the present time is recognized as substrate availability for prostaglandin metabolism, what is the interrelationship between apoptosis in the contribution to the prostaglandin metabolism by the chorion laeve?

Dr. Parmley (Closing). There is a difference between histopathologic reality and clinical reality and this manuscript is a description of an aspect of histopathologic reality. For example, clinical chorioamnionitis is a different entity than histopathologic chorioamnionitis. Many of the criteria that are required to make the diagnosis of clinical choriamnionitis are not present in the cases presented here, but they are not present because it is not the purpose of these observations to make clinical statements. Pathologic chorioamnionitis is the topic under discussion and the gold standard for the diagnosis of pathologic chorioamnionitis is the histologic picture I have just shown you.

As a further illustration, when I made the statement in this presentation that the case was an early example of chorioamnionitis, that statement was made on the

basis of the histologic observation that the leukocytes have not moved very far in the tissue. That is the appropriate pathologic definition of early. It may be totally irrelevant to the clinical diagnosis of early, but it is the appropriate pathologic one.

Many of these examples of histologic chorioamnionitis were in patients who did not show evidence of chorioamnionitis by culture or by symptoms in either mother or infant.

Cases were selected as follows. The placentas from every delivery over a 6-month period were collected. They were processed by a modification of Benirschke's method so that there was a rolled section of fetal membrane available from each placenta. If a review of the records suggested an accurate gestational age then the case was selected for study. Most clinical cases can not be so accurately dated and therefore only a small portion of the total number of placentas was actually examined.

Dr. Roberts asked about natural variation. Whatever the mechanisms for maintenance and termination of pregnancy are, they are undoubtedly characterized by fail-safe mechanisms. That is, they are highly complex and do not depend on any single variable. Consequently, in looking at any single variable, even if it is important, one would encounter a great deal of variation.

We have looked at animals. What the placentas of other mammals show is a similar histology but it is much more acute. That is, in animals this same thing happens but it happens very acutely and over a very short period of time, which tangentially brings me to the question asked by Dr. Malinak.

Apoptosis lasts in the tissue for at most 3 or 4 hours. If you see one example in a tissue section, then the process is taking place very rapidly within that tissue. Placentas near term occasionally show high power fields in which there are two or three examples. I illustrated one stretch of membrane that had multiple examples of it. That means a massive amount of apoptosis is occurring in a very short period of time.

Another question that Dr. Roberts asked was whether factors other than natural cell death can cause apoptosis. The list is a mile long and includes a variety of hormones, perhaps significantly, corticosteroids.

Neutrophils are in the menstruating endometrium as it sloughs, that is, as necrosis is taking place. The apoptosis that takes place in the menstruating endometrium takes place before this time.

Dr. Roberts asked about the relationship of this phenomenon to aging. There is not necessarily such a relationship but the life span of species has been hypothesized to be controlled by a clock similar to the one that is suggested here. A putative stem cell population for the soft tissue might be a sight for such a clock.

Dr. Makowski asked about the site of the membranes. These were randomly selected sections. He also asked about decreased vascularity. Acute decreases in vascularity produce necrosis. Minimal decreases in vascularity were not something we noted.

I agree with the comment from Dr. Shah that these observations raise the possibility that the trophoblast of the chorion laeve is important in the maintenance of pregnancy. I did not speak to that because the suggestion is an indirect one and I do not feel knowledgeable enough to address it. And with respect to the biochemical questions that were raised, I am afraid that this poor old morphologist would make a sad fool of himself if he commented on biochemistry.

Flow cytometric evaluation of epithelial ovarian cancer

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We investigated the prognostic significance of deoxyribonucleic acid content and proliferative activity of tumor cell populations as measured by flow cytometry of the tumor specimens from 115 women with epithelial ovarian cancer. Deoxyribonucleic acid aneuploidy was found in 87 of 115 (76%) of these cancers with a mean deoxyribonucleic acid index of 1.6 and S-phase fraction of 14.7%. The S-phase fraction of the 28 (24%) diploid tumors was 7.0%. Deoxyribonucleic acid ploidy was significantly correlated with survival. S-phase fraction was significantly correlated with ploidy, residual tumor, histology, grade, ascites, time to recurrence, and survival. Diploidy versus aneuploidy were the best discriminating values for deoxyribonucleic acid index and an S-phase fraction of greater or less than 18% for that parameter. Multivariate analysis revealed stage, S-phase fraction, residual tumor, and grade to be independently associated with time to recurrence, and stage, age, S-phase fraction, and largest metastases were factors associated with survival. Deoxyribonucleic acid ploidy did not significantly improve either model. These results suggest that abnormalities of deoxyribonucleic acid content and the proliferative activity of tumor cell populations are reflective of their biologic activity. (Am J Obstet Gynecol 1990;162:1584-92.)

Key words: DNA flow cytometry, ovarian cancer, S-phase fraction

Cancer of the ovary is the leading cause of death among gynecologic malignancies in the United States. Improvements in surgical and chemotherapeutic regimens have had minimal effect on long-term survival. Traditional parameters, such as stage, histologic grade, and tumor burden, have been used to stratify patients into broad prognostic groups.[1] Newer methods, such as the quantitation of deoxyribonucleic acid (DNA) content by flow cytometry, may prove to be more reliable in predicting outcome in ovarian cancer patients. Flow cytometry has been shown to be an objective method of quantitating cellular DNA content and proliferative activity in normal and neoplastic cell populations.[2, 3] Blumenfeld et al.[4] in this country and several investigators[5-10] abroad have reported a strong correlation between ploidy and outcome in women with epithelial ovarian cancer. Only one of these studies discussed ploidy abnormalities in relation to disease progression and time to recurrence.[9] We report the correlation of tumor ploidy, DNA index, and S-phase fraction with other known prognostic factors and on survival and recurrence for all stages of epithelial ovarian cancer.

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Material and methods

Patient data. The medical records of 115 women with epithelial ovarian cancer diagnosed and treated at Northwestern Memorial Hospital between 1978 and 1987 were reviewed with respect to multiple clinical parameters, as shown in Table I.

Pathologic studies. Original histopathologic slides from the above patients were reviewed by one of us (T. M. M.) to ensure that there was adequate tumor tissue in the blocks used for flow cytometry. All cases were reviewed without knowledge of the clinical outcome. After confirming the diagnosis, the cases were classified according to their histologic types as presented by the World Health Organization in 1973[11] and reiterated by Scully in 1977.[12] Tumors of low malignant potential will be reported elsewhere. The tumors were graded as well-differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3) tumors. The well-differentiated carcinomas were characterized by well-formed papillae with fibrovascular cords and no solid components. Grade 2 tumors were partially solid and glandular. The poorly differentiated tumors were recognized when the carcinoma was primarily solid with little or no glandular formation. Mitoses and nuclear pleomorphism were more often seen in high-grade tumors than low-grade

tumors, but these features were not used primarily for grading.

For flow cytometry study the blocks were selected when the entire tissue was represented by the malignancy. In those cases in which benign tissue was noted adjacent to the tumor, the cancerous area was identified by a permanent marker on the paraffin block.

Flow cytometry. The corresponding paraffin-embedded blocks were dewaxed with xylene and rehydrated with a modification of the method originally described by Hedley et al.[13, 14] The tissue was then pepsin treated and resuspended in Hepes-Hanks media. After treatment with ribonuclease I (180 U/ml), the cells were stained with propidium iodide (50 mg/ml) as detailed previously.[14] Cellular DNA content was measured on a Coulter Epics 752 flow cytometer (Coulter Electronics, Hialeah, Fla.). The data were presented as DNA fluorescence histograms from which cell cycle analysis (percent G_1, percent S, percent G_2M), DNA ploidy, and DNA index were calculated. The coefficient of variation about the major G_1G_0 peak on the DNA histogram ranged from 1.0% to 6.9% in these studies (mean, 4.42%). Cases with a coefficient of variation greater than 7.5% were excluded from DNA ploidy and cell cycle analysis. DNA aneuploidy was defined only on the basis of the presence of two distinct G_1/G_0 peaks in the DNA histogram. DNA index was defined as the mean fluorescence of the DNA aneuploid peak divided by that of the DNA diploid peak. This measurement thus provides an indication of the degree of alteration or change in DNA content in relation to diploid cases (DNA index = 1.0). The percentage of S = phase cells was calculated by the MCYCLE software (Phoenix Systems, Inc.) according to a modification of the method of Dean and Jett.[15] Proliferative activity in this investigation was reported on the basis of the percentage of cells in S phase because this calculation has been reported to be a more precise estimate than calculations of the percentage of G_2M.[16]

Statistical methods. Time to recurrence and survival were calculated from the date of primary operation. The tests used to compare DNA index and S-phase fraction with clinical parameters, such as stage, grade, histology, and residual tumor, were χ_2 and analysis of variance.[17] Kaplan-Meier product limit estimates,[18] Breslow's generalized Wilcoxon test,[19] and Cox regression analysis were used to evaluate the association of S-phase fraction and the other factors to recurrence and survival.[18] Hazard ratios indicate the change in the risk of recurrence or death per unit change in percent S phase. Stepwise Cox multivariate regression analysis was used to assess the relative order of importance of clinical parameters to recurrence and survival time. Data analysis was performed with BMDP statistical software.[20] Statistical significance was defined as values of $p < 0.05$.

Table I. Patient data

- Personal history
  - Age
  - Race
  - Gravidity/parity
  - Menarche
  - LMP/menopause
  - Cancer history
  - Contraceptive use
  - Cancer family history
- Surgical data
  - Primary operation
    - Primary tumor diameter
    - Largest metastasis diameter
    - Size largest residual tumor
    - Structures left
    - Complications
    - Ascites
    - EBL
    - Transfusion
  - Second-look procedure
    - Largest tumor diameter
    - Size largest residual tumor
    - Structures left
    - Complications
    - Ascites
    - EBL
    - Transfusion
- Histopathologic data
  - Stage
  - Grade
  - Histology
  - Ca 125
  - Estrogen receptor
  - Progesterone receptor
  - DNA index
  - Cell cycle analysis
- Chemotherapy
  - Dates
  - Disease status
  - Weight
  - BSA
  - Ca 125
  - Dosages
  - Toxicity

LMP, Last menstrual period; EBL, estimated blood loss; BSA, body surface area.

Results

Of the 115 patients evaluated, 17 (15%) had stage I disease according to International Federation of Gynecology and Obstetrics criteria, 13 (11%) had stage II disease, 61 (53%) had stage III, and 24 (21%) had stage IV disease. After primary tumor debulking, 29 (25%) patients were left with no residual tumor, 43 (37%) had implants <2 cm, and 38 (33%) had residual tumor implants >2 cm. The correlation of stage and residual tumor is shown in Table II. As seen in Table III, most cancers were serous histologically and poorly differentiated.

DNA aneuploidy as defined by a DNA index other than 1.0 was found in 76% of these tumors (87/115). The mean ± SE DNA index of the aneuploid cancers

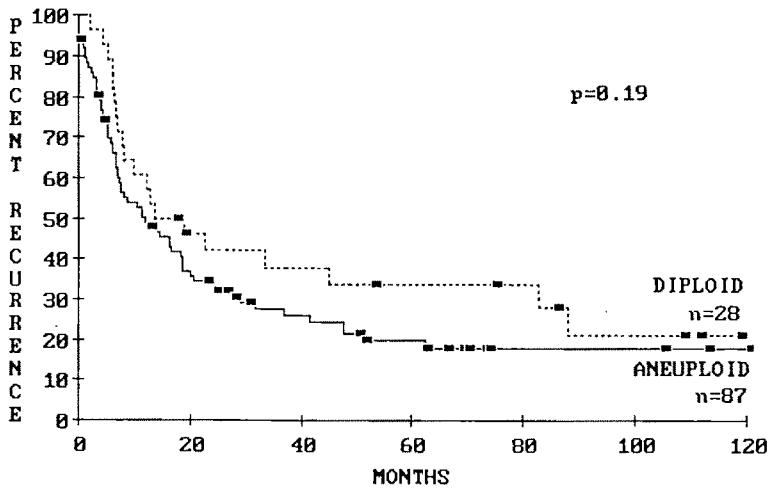


Fig. 1. Time to recurrence product limit curves for diploid (n = 28) versus aneuploid (n = 87) DNA index, p = 0.04.

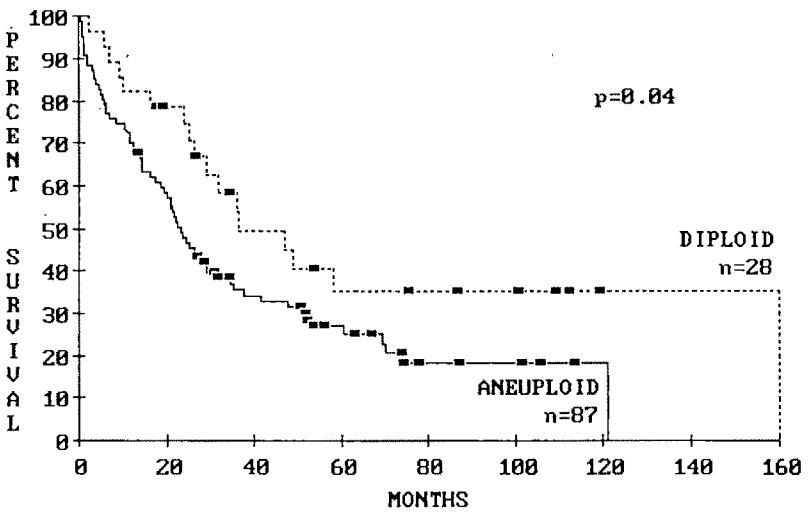


Fig. 2. Product limit survival curves for diploid (n = 28) versus aneuploid (n = 87) DNA index, p = 0.19.

Table II. Stage versus residual tumor

	Residual tumor								*Total*	
	None		*<2 cm*		*>2 cm*		*Unknown*			
Stage	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	15						2		17	15
II	10		2		1				13	11
III	4		33		22		2		61	53
IV			8		15		1		24	21
Total	29	25	43	37	38	33	5	4	115	100

Residual tumor was not described in five patients. χ^2, p = 0.0001.

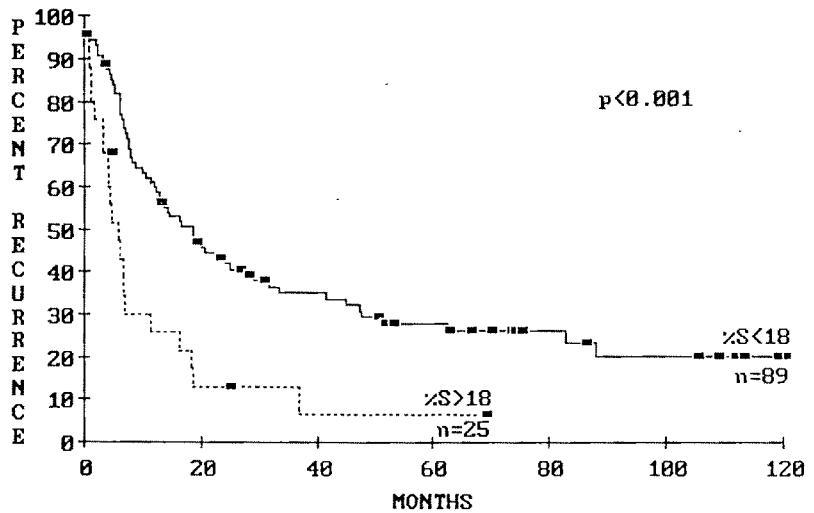


Fig. 3. Time to recurrence product limit curves for S-phase fraction <18% (n = 89) versus > 18% (n = 25), $p < 0.001$.

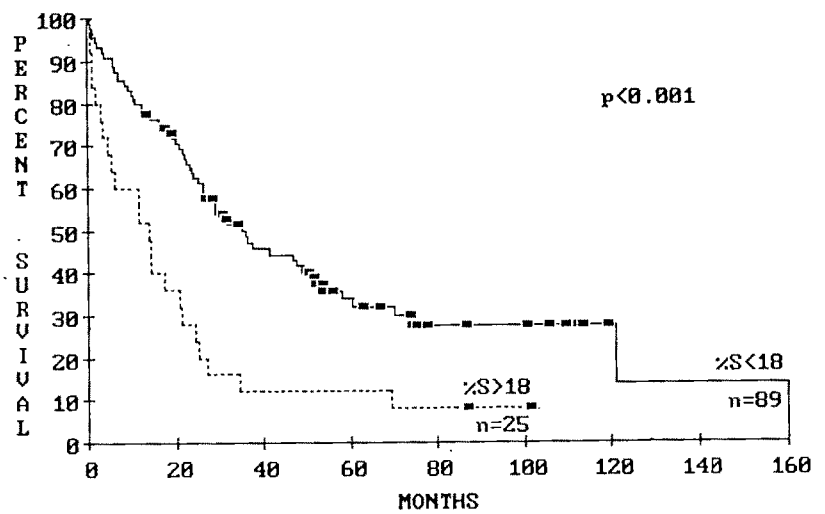


Fig. 4. Product limit survival curves for S-phase fraction < 18% (n = 89) versus >18% (n = 25), $p < 0.001$.

was 1.60 ± 0.04 and the S-phase fraction of cells 14.7% ± 0.9%. The S-phase fraction of the 28 (24%) diploid cancers was 7.0 ± 0.8. Aneuploidy and S-phase fraction were correlated ($p < 0.0001$). The results of flow cytometry in relation to the factors listed in Table I were analyzed and correlated ones are displayed in Tables IV through VIII. Histologic type and grade correlated with tumor ploidy (Tables VI and VII). S-phase fraction was significantly correlated with residual tumor, histologic type, grade, and ascites (Tables V through VIII).

With a minimum follow-up time of 30 months, 83 of 115 patients have died (72 of cancer, 8 of complications, and 3 of other causes). Of the remaining 32 patients, 24 are alive without evidence of disease and 8 are alive with disease. Median time to recurrence was 13 months and median length of survival was 26 months.

Tumor ploidy and S-phase fraction were correlated with time to recurrence and survival. DNA ploidy correlated with survival ($p = 0.04$), whereas S-phase fraction was correlated with time to recurrence (hazard ratio = 1.04, $p = 0.0008$) and survival (hazard ratio = 1.04, $p = 0.0013$).

Time to recurrence and survival time versus DNA index were evaluated by product-limit survival analysis. Tumor diploidy versus aneuploidy was the best prog-

Table III. Histologic type versus grade

	Grade								Total	
	1		2		3		Unspecified			
Histologic type	No.	%	No.	%	No.	%	No.	%	No.	%
Serous	4		24		38		1		67	58
Endometrioid	7		6		10				23	20
Mucinous	6		4						10	9
Clear cell			1		2		1		4	3
Undifferentiated			1		10				11	10
Total	17	8	36	33	60	59	2	2	115	100

χ^2, $p < 0.0001$.

Table IV. Stage, DNA ploidy, and S-phase fraction

	Aneuploid		% S-phase fraction
Stage	No.	%	(mean ± SE)
I	10/17	59	9.5 ± 2.1
II	9/13	69	10.2 ± 1.9
III	49/61	80	13.1 ± 0.9
IV	19/24	80	15.9 ± 2.1
	$p = 0.29$		$p = 0.059$

Table V. Residual tumor, DNA ploidy, and S-phase fraction

	Aneuploid		% S-phase fraction
Residual tumor	No.	%	(mean ± SE)
0 cm	20/29	69	9.7 ± 1.5
≤2 cm	34/43	79	13.8 ± 1.2
>2 cm	30/38	79	15.0 ± 1.4
	$p = 0.55$		$p = 0.027$

Table VI. Histologic type, DNA ploidy, and S-phase fraction

	Aneuploid		% S-phase fraction
Histologic type	No.	%	(mean ± SE)
Serous	56/67	84	14.9 ± 1.0
Mucinous	7/10	70	9.1 ± 2.4
Endometrioid	13/23	56	10.7 ± 1.8
Clear cell	2/4	50	5.1 ± 0.7
Adenocarcinoma	9/11	82	10.9 ± 2.6
	$p = 0.069$		$p = 0.017$

nostic discriminator for DNA index. The median time to recurrence was 14 months for the diploid tumors and 11 months for the aneuploid tumors ($p = 0.19$) (Fig. 1). The median patient survival was 36 months

Table VII. Grade, DNA ploidy, and S-phase fraction

	Aneuploid		% S-phase fraction
Grade	No.	%	(mean ± SE)
1	9/17	53	7.2 ± 1.7
2	27/36	75	13.5 ± 1.4
3	49/60	82	14.3 ± 1.0
	$p = 0.053$		$p = 0.006$

Table VIII. Ascites, DNA ploidy, and S-phase fraction

	Aneuploid		% S-phase fraction
Ascites	No.	%	(mean ± SE)
Present	52/64	81	14.5 ± 1.1
Absent	25/37	68	11.0 ± 1.2
	$p = 0.19$		$p = 0.042$

for the diploid tumors and 23 months for aneuploid tumors ($p = 0.04$) (Fig. 2). An S-phase fraction of 18% was the best prognostic discriminating level of that variable. The median time to recurrence was 17 months for those fractions <18% and 5 months for those >18% ($p < 0.001$) (Fig. 3). The median survival was 32 months for those <18% and 12 months for those >18% ($p < 0.001$) (Fig. 4).

The other parameters listed in Table I were correlated with outcome by univariate analysis. Stage and residual tumor, the diameter of the largest metastases, ascites, and size of residual tumor were significantly associated with time to recurrence and survival ($p < 0.001$). Primary tumor diameter was associated with time to recurrence ($p = 0.04$). Survival was also assocociated with age ($p = 0.0097$).

On the basis of results of univariate analysis and other studies,[1] 10 factors were chosen for analysis by Cox multivariate stepwise regression. The variables that

were independently associated with time to recurrence were stage, S-phase fraction, residual tumor, and grade (Table IX). There was no significant improvement in the model by the addition of DNA ploidy. However, stage, age, S-phase fraction, and largest metastasis diameter were independently associated with survival (Table X). DNA ploidy did not significantly improve the survival model.

Table IX. Cox multivariate analysis of time to recurrence

Step	*Variable*	*p to Enter*
1	Stage	<0.0001
2	S-phase fraction	0.0022
3	Residual tumor	0.005
4	Grade	0.02
5	Chemotherapy type	0.22
6	Ascites	0.21
7	Age	0.27
8	Ploidy	0.32
9	Histologic type	0.54
10	Metastasis diameter	0.52
11	Primary tumor diameter	0.84

Table X. Cox multivariate analysis of survival

Step	*Variable*	*p to Enter*
1	Stage	<0.0001
2	Age	0.003
3	S-phase fraction	0.01
4	Metastasis diameter	0.03
5	Ascites	0.07
6	Chemotherapy type	0.05
7	Grade	0.14
8	Ploidy	0.10
9	Residual tumor	0.41
10	Histologic type	0.52
11	Primary tumor diameter	0.67

Comment

The application in recent years of DNA flow cytometry has provided supplemental information regarding prognosis for women with epithelial ovarian cancer. Our results demonstrate that tumor ploidy and S-phase fraction are prognostic factors in epithelial ovarian cancer. This is a consistent finding in other recent reports,[5-10] although the importance of flow cytometry results in multivariate analysis varies from study to study. In our analysis, S-phase fraction was predictive of recurrence and survival, with 18% being the most sensitive predictor for that variable. This suggests that proliferative activity significantly influences the clinical behavior of these tumors, such that tumors with a high percentage of actively dividing cells behave in a more aggressive manner.

Review of the literature reveals a considerable range in the frequency of aneuploidy detected in epithelial ovarian tumors, from a low of 52% to a high of 81%. Factors that may influence the frequency of aneuploidy include the stage of disease (i.e., inclusion of early stage disease), the type of tissue analyzed (i.e., fresh versus paraffin blocks), the area of tumor analyzed, and the sensitivity of the techniques and instrumentation used. For this study, the original histopathologic slides were reviewed by a single individual (T.M.M.) without knowledge of clinical outcome; areas of high tumor density were marked for flow cytometry. This process may be more time-consuming than the use of fresh tissue or random blocks, but we believe that it lends consistency to our results and provides an accurate assessment of tumor aneuploidy in our patient population.

Of the recent studies in the literature, only Rodenburg et al.[9] have addressed the issue of flow cytometry on progression-free interval. In their analysis, as in ours, ploidy was dropped out as an independent prognostic factor in multivariate analysis. However, S-phase fraction, stage, residual tumor, and grade were predictive of time to recurrence and survival by multivariate analysis in this study.

The dismal survival of patients with aneuploid tumors and those with high S-phase fraction suggests inherent differences exist between these tumors and diploid tumors. Although flow cytometry quantitates cellular DNA content and proliferative activity, it can provide an indirect measure of qualitative differences in cellular function and may be useful in understanding the biologic characteristics of malignancy. Chromosomal instability and gene amplification cause abnormalities in DNA content that can be detected by flow cytometry. There is evidence that the latter, at least, directly confers drug resistance to some cells.[21] In addition, DNA rearrangements may contribute to drug resistance and increased malignant behavior by altering expression of single genes, such as enzymes and other proteins involved in DNA repair and drug uptake. Increasing aneuploidy and S-phase fraction with disease stage suggest an ongoing process leading to accumulation of lesions, both at the chromosomal and gene level, which in turn contributes to further invasive behavior and drug resistance. This is consistent with the Goldie-Coldman[22] hypothesis of the genetic origin of drug resistance and helps to explain the biologic behavior of epithelial ovarian cancer as well as the usefulness of flow cytometry in predicting response to therapy, progression-free interval, and overall survival in this disease.

We concur with investigators such as Wils et al.,[10] who suggest that the results of flow cytometry be used in

conjunction with other prognosticators, such as clinical stage, to tailor treatment protocols based on risk assessment. This may be useful for two groups of patients, particularly those with favorable prognostic variables, to avoid unnecessary treatment morbidity, and those with an especially poor prognosis to target for investigational or no therapy.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Christopher J. Jolles, Salt Lake City, Utah. The flow cytometer has become an important research tool in clinical oncology since the instrument became readily available 5 to 7 years ago. This complex device has provided some of our first insights into the cellular heterogeneity of tumors. To perform this procedure, an appropriately prepared and labeled cell suspension is analyzed to generate a histogram of single-cell label intensity. Although many different cellular components may be labeled, the initial clinical articles in this field focused on individual cellular DNA content. This enables the cytometrist to determine the fraction of tumor cells in each phase of the cell cycle and the fraction of cells with aneuploid chromosomes. Last year, Kallioniemi et al.[1] and Klemi et al.[2] reported series of 157 ovarian tumors showing correlation between increased nuclear aneuploidy, increased histologic nuclear grade, and decreased patient survival.

The authors are to be congratulated for their work in an area that is in the forefront of oncologic research. They have investigated their hypothesis that abnormal DNA flow cytometry is correlated with known poor prognostic factors in ovarian cancer. Tumor grade is perhaps the most important known pathologic prognostic feature in this disease. Unfortunately, they indicated that they were not able to demonstrate a correlation between aneupoidy and tumor grade. They attributed this result to the small number of patients in their report. As pointed out by Klemi et al.,[2] the term "aneuploid" has been defined in many ways by different flow cytometrists. The difficulty in defining a spectrum of clinical behavior may relate to the fact that >10% of benign cysts are also noted to be "aneuploid" by this technique and 93% of all malignant tumors in the authors' series were aneuploid. The authors did not define the formula used to calculate the "DNA index" in their article. It would be important to know if their index of aneuploidy was designed to weigh all cellular DNA contents equally or if increased weight was given to more severely aberrant cell populations and decreased weight given to near diploid cell populations. Indeed, this may explain the lack of correlation with tumor grade.

To ensure that tumor measurements accurately reflect aneuploidy, it is important to control for many potential sources of error. For example, falsely elevated DNA index results can be obtained when flow cytometry is performed on ovarian cancer metastases instead of primary tumors.[3] Although the authors used

ribonuclease treatment to decrease fluorescent interference from the increased ribonucleic acid content of tumor cells, additional control of this variable can be obtained by restricting analysis to nuclear suspensions. The expanded "S-phase" population of tumor cells can also cause false-positive results and this can be controlled by in vitro labeling of fresh tissue with radiothymidine and by accepting only sharp and well-defined G_0/G_1 peaks rather than broad-based background fluorescence in the range of 1.0 to 2.0. In contrast, falsely decreased DNA index results commonly occur when specimens are not controlled for their variable content of normal supporting mesothelial and connective tissue cells. This is commonly performed by gradient centrifugation of disaggregated cells before cell sorting. If this separation is not done, cell sorter results may reflect connective tissue content and thereby mask correlation between aneupoidy and tumor grade.

When the many variables are controlled, flow cytometry will add greatly to our understanding of cancer. Cytometric testing is presently in clinical application in many community-based hospitals throughout the country. When new technology is applied, it is important to determine how it is best used to modify our treatment approach. I am not aware of the evidence referred to by the authors that flow cytometry is more sensitive than histopathologic analysis in the detection of cancer, and I do not understand how this test can be used to define a tumor stage. On the basis of data presented and in view of these multiple experimental variables, I would ask the authors in what specific instances a determination of tumor aneuploidy should influence current patient management.

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DR. JOHN R. DAVIS, Tucson, Arizona. For those in the audience unfamiliar with flow cytometry methods, a point of clarification is appropriate. Tissue blocks were selected for flow cytometry methodology analysis based on totality of tumor involvement in the sample. However, all aneuploid cases were defined on the basis of the presence of two G_0/G_1 peaks. One is the aneuploid clone; the other is normal host tissue from connective tissue, perhaps with an inflammatory component. The ubiquity of normal cells is important because an internal normal control is automatically available.

This article fulfilled its goals in terms of testing DNA features in epithelial ovarian cancer by flow cytometry with regard to survival and time to recurrence. For the latter, flow cytometry data were not as useful in prediction as were clinical data of stage and largest metastasis. The flow cytometry data do aid in survival prediction in terms of S-phase fraction and whether tumor is diploid or aneuploid. Prior literature findings were confirmed.

Is aneuploidy or diploidy more important than numerical value of DNA index? Although controversial in cases of cervical cancer,[1] ploidy in this article had greater value than DNA index.

Should flow cytometry be routine in ovarian carcinoma study? The authors suggest its use in conjunction with accepted prognostic factors for stratifying favorable or unfavorable outcomes. In breast[2] and lung[3] neoplasia, a major flow cytometry role is in early-stage neoplasms (small size and lymph node negative). Abnormal DNA content serves to predict outcome and a basis for management strategies.

Perhaps this will be the eventual role of flow cytometry in ovarian cancer. Patients with early-stage and low-grade carcinomas may be better subjects for routine flow cytometry than the entire group (with mostly late-stage and mid- to high-grade tumors).

I have several questions for Dr. Barnabei. (1) In selection of paraffinized tissue for flow cytometry analysis, was the whole block used or a 50 μm slice? (2) The initial draft of the article consisted of 30 μm cases, 28 of which were aneuploid. In the final draft an additional 31 cases were included, 20 of which were aneuploid. Aneuploid rates in the two sets were 93% and 65%, respectively. Were case acquisitions consecutive or selected for better balance in range?

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DR. MURRAY J. CASEY, Omaha, Nebraska. I do not want to take the time of a formal discussion, but in experimental tumors the labeling index is considered to be a measure of the S phase, which in turn is the proportion of cells undergoing proliferation. In experimental mouse tumors, metastatic rate has been shown to be related to the proliferation rate.

For clinicians tumor grade has been a disappointing method of predicting whether or not the tumor would metastasize and a poor measure of the clinical outcome. We have had to rely on such crude measures as size of tumor, adhesions, spillage, external excrescences, etc. to prognosticate outcome. Flow cytometry and labeling now allow us to look at fresh tumors and assess the proportion of cells in the S phase. I would suggest to the authors that as a step in this direction, they restudy

the stage I tumors and determine the proportion of each tumor that was in the S phase, and determine if there is a correlation with the crude clinical findings reported on the operative report and the clinical outcome of those cases.

If, in fact, there was a direct correlation, then I believe that clinical laboratories would be prompt to adopt flow cytometry and the determination of labeling index, for instance, as a measure of determining whether or not patients with stage I tumors should or should not receive chemotherapy.

Dr. Eduard Eichner, Cleveland, Ohio. In the 1940s and 1950s I did lymphatic studies on these types of cases. One point of interest in our preliminary work of learning the size of material was the dye we used. We took different sizes of the dye to inject into the ovary and other organs and found that the real microsize, a millimeter or less, of the dye material went into the lymph nodes and then through the veins directly into the general circulation, which means that the small cell that is probably rapidly growing will spread fast.

The larger lumps of dye reached the node and stopped there, blocked the lymphatics, and then went backward. This type of study was reported then, so its use is a possibility.

Dr. Robert Carpenter, Houston, Texas. I have only limited knowledge of flow cytometry. If live tissue is compared with paraffin-embedded tissue, what is the sensitivity and specificity of the outcome? Will it have similar percentages, peaks, etc., or will there be a significant loss? If there is loss, will that then correlate with what you were addressing in your initial question?

Dr. Barnabei (Closing). Dr. Jolles was very precise; I was afraid somebody was going to ask me to extrapolate more on tumor grade. I think that is where the interest in some of this research lies.

I would like to comment on the correlation of aneuploidy and grade. As Dr. Weiland mentioned in a previous discussion, morphometry does not equal function. We have been very dependent on grade for a prognosis in such patients, and I think that grade may only be the large picture. We are gradually honing in on smaller aspects, and now we are studying content. As most of you know, we are also examining the gene level, oncogene expression, and those types of factors. We are getting more detailed in the ability to predict the outcome in these patients by utilizing factors other than tumor grade.

In almost all studies on ovarian cancer, when studied in multivariate analysis, grade becomes nonsignificant compared with other factors, including S-phase fraction and other aspects of flow cytometry.

Dr. Davis answered most of Dr. Jolles' questions about management, and I concur with what Dr. Casey said; perhaps the most useful aspect of flow cytometry at this point may be for analysis of early-stage cancers with low DNA content and low S-phase fraction to avoid significant morbidity in overzealous treatment.

I believe we did use nuclei and not cell suspensions for this study. The coefficient of variability for the DNA peaks ranged from 1 to about 6; peaks with a variability >7.5 were excluded.

In the studies I have seen on ovarian cancer, the aneuploidy percentage in fresh tissue is less than that found in paraffin-embedded tissue, although the peaks are actually clearer. The coefficient of variability is better, but there is a decreased percentage of aneuploidy. That is why I think our process of choosing tumors on the basis of their high tumor density is more indicative of the amount of aneuploidy in these tumor cells.

Finally, I think that until we are more successful in identification of patients with ovarian cancer before their disease is advanced, we must use whatever other information is available to improve survival in these women. I think the application of DNA flow cytometry will have clinical usefulness in the future for the evaluation and treatment of patients with epithelial ovarian cancer.

The Green Bay cesarean section study

I. The physician factor as a determinant of cesarean birth rates

Robert K. DeMott, MD, and Herbert F. Sandmire, MD
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This study was designed to identify the determinants of cesarean birth rates. The study population included all 1030 cesarean deliveries performed on singleton pregnancies by 11 obstetricians practicing at two Green Bay hospitals from 1986 through 1988; 1076 control patients with vaginal deliveries were selected for comparison purposes. The 1030 cesarean deliveries represented 14% of the 7335 singleton deliveries that occurred during the study period. Individual physician cesarean rates ranged from 5.6% to 19.7%. Cesarean rates for physician groups ranged from 9.8% to 18%. The variances in cesarean rates among individual and groups of physicians were not attributable to patient obstetric risk factors, socioeconomic status, service status, or duration of the physician's practice. Higher cesarean rates did not result in better neonatal outcome. Individual physician practice style was the only apparent determinant of cesarean rates for the 11 obstetricians. Current cesarean rates can be substantially reduced without sacrificing fetal and newborn safety. (AM J OBSTET GYNECOL 1990;162:1593-602.)

Key words: Cesarean birth rates, cesarean birth morbidity, physician factor as a determinant of cesarean rates

During the past 15 to 20 years cesarean section rates in the United States have increased from approximately 5% in the late 1960s to more than 25% in 1988.[1] Various factors explain this increase, reasons that usually are based on presumed improvement of neonatal outcomes without offsetting increased maternal morbidity and mortality. Interestingly, some centers have achieved similar reductions in perinatal mortality without dramatic increases in cesarean section rates or with rates substantially below those generally existing in the United States.[2, 3]

Proponents of increased cesarean rates have cited safety of the operation as a result of medical and surgical advances since the late 1960s and early 1970s. Nevertheless, we are unaware of any advances that resulted in increased cesarean section safety in the 1980s compared with the earlier period. Some authors consider present cesarean rates inappropriately high.[1, 3-7] Some have cited the individual practice style of the obstetrician as a strong determinant of cesarean rates.[8] Although we agree that the rates are high, we do not know *what* rate is optimal. Thus we designed this study to examine factors that influence route of delivery decisions, and the effect of the delivery route on maternal and newborn outcomes. Our study design permits us to evaluate not only individual practice differences, but also other variables that influence the choice of delivery route. The data will be further analyzed in relation to specific pregnancy and labor characteristics that influence route of delivery in the following complications: failure to progress, breech presentation, and fetal distress. These data will be the subject of future articles.

Material and methods

The study population included all singleton cesarean deliveries performed on private patients* by 11 board-certified obstetrician-gynecologists who practiced exclusively and full-time (over 400 deliveries) at two Green Bay hospitals from 1986 through 1988. Control patients with vaginal deliveries consisted of the next singleton vaginal delivery for that obstetrician after the index cesarean delivery. The total number of singleton deliveries was 7335; there were 1030 cesarean sections (14%). Those 1030 cesarean section and 1076† control patients' records were reviewed by labor and delivery nurses who recorded pertinent findings on data re-

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*All Green Bay obstetric patients have private status, regardless of insurance or Medicaid status.

†After initial data collection, twin and triplet gestations were excluded from this study analysis. This resulted in slightly more control patients (vaginal deliveries) than cesarean deliveries in this singleton study. Because of the random nature of selection, no efforts were made to equalize the numbers in each study group.

Table I. Cesarean section rates for individuals and groups of physicians*

Physician cesarean rate group	*Physician No.*	*No. of cesarean sections*	*Total No. of deliveries*	*Percentage*	
				Physician	*Group (mean)*
Low	1	23	408	5.6	
	2	68	758	9.0	
	3	78	684	11.4	9.8
	4	70	591	11.8	
		239	2441		
Mid	5	64	504	12.7	
	6	70	522	13.4	13.4
	7	131	946	13.8	
		265	1972		
High	8	65	412	15.8	
	9	178	1066	16.7	
	10	123	632	19.5	18.0
	11	160	812	19.7	
		526	2922		
≥TOTAL		1030	7335		14.0

*Singleton pregnancies for 36 months (Jan. 1, 1986 through Dec. 31, 1988).

trieval sheets. Similarly, the nurses reviewed all newborn records, except neonatal intensive care unit admissions; neonatal intensive care unit patient records were reviewed by the authors. Because of the small numbers of certain morbidities for newborn infants delivered by any single obstetrician (such as neonatal intensive care unit admissions), we elected to group the 11 physicians into low, middle, and high groups based on cesarean section rates. The assignment of the physicians to different cesarean rate groups was somewhat arbitrary but did result in all groups having a large number of deliveries.

One of the two hospitals in the study serves as the perinatal referral center for 13 surrounding northeastern Wisconsin and upper Michigan counties. A neonatologist attends all cesarean and selected vaginal deliveries, depending on the anticipated needs of the neonate. Because the 11 obstetricians in the study are consultants for that center and rotate as the on-call consultant for equal time periods, patient characteristics should not differ significantly among the physicians. Despite this, we analyzed those characteristics that have been reported to influence cesarean rates and neonatal outcomes for variations among individual physicians, groups of physicians, and cesarean versus vaginal delivery.[3, 8] Maternal age, parity, race, socioeconomic status, service status, insurance status, and county of residence failed to demonstrate significant differences in patient profiles. In addition, mean gestational age at delivery and mean birth weights did not significantly vary among physicians. Low- and high-birth-weight distribution also was uniformly distributed among physicians and physician groups. There was no difference in the mean number of years in practice in comparison of the low and high physician cesarean rate groups (low, 13%; middle, 20%; high, 13.5%). Continuous electronic fetal monitoring was used in a very high percentage of the laboring patients in the study and did not vary in frequency of use among individual physicians and physician groups.

We analyzed the data with PROC FREQ and PROC GLM programs in the SAS package. Relevant continuous variables such as infant weight or Apgar scores were subjected to two-way analysis of variance to examine interaction between physician groups and mode of delivery. For example, we asked whether the mean Apgar score for infants delivered by cesarean section differed from the mean score for vaginal deliveries by the same amount for all groups of physicians. In general, it did differ by the same amount for all the variables examined. When the data represented as frequencies (for example, frequencies of very large and very small babies), two-way tables of frequencies were analyzed with χ^2 to determine if physician groups differed in the percentages of very-low-birth-weight or macrosomic infants, with separate analyses for cesarean and vaginal delivery. We found no relationships between relevant variables and physician groups.

Results

Individual physician cesarean rates range from a low of 5.6% to a high of 19.7%. The mean rate for the entire study population was 14.0% (Table I).

Table II demonstrates the mean total, primary, and repeat cesarean rate for singleton pregnancies for the three groups of physicians. The total range was 9.8% to 18.0%. There are statistically significant increases in both the rates of primary and repeat cesarean sections when the high and low physician rate groups are compared.

Table III demonstrates the primary cesarean rate for singleton pregnancies for the three physician groups. For all indications combined, the difference between the high and low physician rate groups was statistically significant. Similarly, the high group performed significantly more cesarean sections for each individual indication. The distribution of cesarean section indications was similar for each physician and each physician group. For example, no one physician group had a disproportionately larger number of breech presentations or repeat cesarean sections (Table IV). One hundred thirty-two of the 1030 (12.8%) patients with cesarean deliveries and 119 of the 1076 patients (11.1%) with vaginal births had their health care costs paid by Medicaid; this difference was not statistically significant ($\chi^2 = 1.53$).

Neonatal outcome. Analysis of neonatal outcome included both the method of delivery and cesarean rate. There were no differences in the proportion of low Apgar scores, for vaginal and cesarean deliveries combined, among the different physician groups (Table V). When score were averaged over all physician groups, 1-minute Apgar scores were 0.5 units lower (7.39 vs 7.89) for infants delivered by cesarean versus vaginal delivery. The difference was 0.27 units lower (8.75 vs 9.02) for the 5-minute Apgar score. The fact that the interaction analysis of Apgar scores between cesarean and vaginal delivery failed to achieve statistical significance indicated that the differences were constant over the three physician groups.

The immediate need for neonatal resuscitation, by bag and mask or intubation, did not differ between physician groups for either cesarean or vaginal delivery (Table VI). One hundred eighty-seven infants (9%) in our study population of 2106 singleton deliveries were admitted to the neonatal intensive care unit (Table VI); 136 of these admissions followed cesarean delivery. For infants delivered by cesarean section, admission to the neonatal intensive care unit occurred slightly more frequently in the low cesarean rate group of physicians, but the difference is not statistically significant. A comparison of median length of stay in the neonatal intensive care unit suggests no effect of either mode of delivery or physician group (Table VI).

Length of respirator use was the same for all three physician groups (Table VI). When low-birth-weight infants were excluded from analysis, transient tachypnea ("wet lung") occurred 4.5 times more frequently after cesarean section compared with vaginal birth (41 cases versus 9). All five infants with birth weights >4500 gm who were admitted to the neonatal intensive care unit were delivered by cesarean section. Neonatal seizures, respiratory distress syndrome, apnea, intraventricular hemorrhage, pneumonia, sepsis, meconium aspiration syndrome, hypocalcemia, hypoglycemia, hyperbilirubinemia, wet lung, and death occurring primarily to infants admitted to the neonatal intensive care unit, either occurred too infrequently to statistically analyze or occurred with equal proportion in all groups of physicians regardless of cesarean rate (Table VII).

There were 17 neonatal deaths (8.1 per 1000) and five stillborn deliveries (2.4 per 1000) in the study population. This compares favorably with our overall perinatal mortality rate of 9.2 per 1000 infant births at the two study hospitals in the 3-year study period (60 neonatal deaths, 31 stillbirths, 9848 infant births over 20 weeks' gestation). Fourteen of the 17 infants who died and one of the 5 stillborn infants were delivered by cesarean section.

Of the 17 neonatal deaths, four occurred in infants with hypoplastic lungs (usually associated with prolonged rupture of membranes), five showed signs of Potter's syndrome, two had other congenital defects

Table II. Cesarean section rates for all singleton deliveries (N = 7335)*

	Physician group		
	Low	*Mid*	*High*
Total deliveries	2441	1972	2922
Category (% of all deliveries)			
Primary†	6.7	9.0	10.9
Repeat	3.1	4.4	7.1
Mean	9.8	13.4	18.0
SD	±0.6	±0.8	±0.7

*All deliveries occurred between Jan. 1, 1986 and Dec. 31, 1988.

†Includes patients with a prior history of cesarean delivery who were allowed to labor, but were delivered by cesarean section for indications other than previous cesarean section.

Table III. Primary cesarean section rate for singleton deliveries*

	Physician group		
	Low	*Mid*	*High*
Total deliveries†	2365	1886	2715
Indication (% of all deliveries)			
Failure to progress	2.3	3.1	4.3
Breech	1.9	2.3	3.1
Fetal distress	1.6	1.4	2.2
Other	1.0	2.6	2.2
>TOTAL	6.8	9.4	11.8

*All deliveries occurred between Jan. 1, 1986, and Dec. 31, 1988.

†Patients who had scheduled repeat cesarean sections were excluded from the numerator in the calculation of primary cesarean rates. The total rates here are therefore different from those presented in Table II.

Table IV. Distribution of singleton cesarean sections by physician cesarean rate groups

Primary indicator for cesarean section	*Physician group*		
	Low	*Mid*	*High*
% of Primary cesarean deliveries			
Failure to progress	34	33	36
Breech presentation	28	25	26
Fetal distress	23	15	19
Other	15	27	19
	100	100	100
% of All cesarean deliveries			
Primary	68	68	61
Repeat	32	32	39
	100	100	100
Total cesarean section Rate (%)	9.8	13.4	18.0

incompatible with life, four died of severe prematurity, and two died of complications as a result of placental abruptio and sepsis, respectively. Eight of the 17 pregnant women whose infants died were transferred to our perinatal center from outlying communities on the suspicion of adverse perinatal outcome.

Maternal outcome. The incidence of spontaneous vaginal delivery was 93%. There were no significant differences in the low rate of either forceps or vacuum-assisted deliveries between any of the physician groups. Postpartum complications were also low in our study population. Cesarean deliveries were complicated by endometritis in only 1.8% of cases. Hemorrhage requiring transfusion and unexplained febrile illness (100.4° F occurring twice after the first postpartum day) occurred in 1.9% and 2.2% of cases, respectively. Overall, 84% of cesarean cases had no complications (major or minor). There were no statistically significant differences in the rates of these complications among physician groups.

As expected, vaginal deliveries resulted in very low rates of complications. For example, there was only one case of endometritis among women with vaginal deliveries. After vaginal deliveries hemorrhage occurred in only 1.6% of cases. Overall, 96% of women with vaginal deliveries reported no complications.

Comment

These results indicate that the major determinant of route of delivery is the individual practice style of each physician. The variances in cesarean rates among individuals and groups of physicians are not attributable to patient obstetric risk factors, socioeconomic status, service status, or duration of the physician's practice.

Contrary to a recent report by Gould et al.,[9] a higher proportion of poor patients in out study (Medicaid) had cesarean sections than the more affluent patients, although the difference is not significant. Gould et al. indicated that their observed differences in cesarean rates "may reflect the different settings (service status) in which the rich and poor receive their obstetrical care. The poor are more likely to give birth in public hospitals and have their health care costs covered by Medicaid, and are less likely to have private physicians." The results of our study demonstrate that the socioeconomic status of the patient is not a determinant of cesarean section rates. It is probable that the lower cesarean rate for poor patients reported by Gould et al. is a result of the individual physician factor associated with the differences in health care settings in which the rich and poor receive their obstetric care. Thus the lower socioeconomic status serves as a proxy for the difference in health care setting as a cause for lower cesarean rates.

The overall cesarean rate (14%) in our study population is below U.S. rates (25%) for the study period. This reduces the magnitude of possible differences in cesarean rates between low and high individual physicians and groups of physicians. For example, Goyert et al.[8] reported a range of 19.1% to 42.3% (mean, 26.9%) among 11 physicians, a difference of 23.2%. The individual physician range in our study was 5.6% to 19.7%, a difference of only 14.1%.

Some researchers have offered improved neonatal outcomes as justification for the fivefold increase in cesarean rates that have occurred during the past 15 to 20 years. Our data generally indicate less favorable newborn outcomes with cesarean compared with vaginal deliveries. This was particularly noted in the frequency of "wet lung" syndrome in term infants (4.5-fold increase). However, because cesarean deliveries occur more frequently in pregnancies with greater newborn risks (very low and very high birth weights), less favorable outcomes would be expected.

The main focus of this study was to determine the effect of cesarean rates on neonatal outcome when neonates from both cesarean and vaginal births were considered. Do newborns delivered by physicians with high cesarean rates fare better than newborns delivered by physicians with low cesarean rates? Our data clearly demonstrate no difference in the condition of newborn infants from cesarean and vaginal births comparing low to high cesarean rate physician groups (Tables V, VI, and VII). Therefore the physicians with low cesarean rates do not place infants at greater risk by the avoidance of many cesarean sections in their patient population. Other authors have reported similar findings.[2, 3, 8]

The fear of professional liability claims produces a substantial impact on delivery decisions.[10, 11] Most of the 11 physicians have had one or more liability claims filed against them. For the younger physicians who have not,

Table V. Distribution of Apgar scores by physician cesarean rate groups for combined vaginal and cesarean deliveries

Physician cesarean rate group	*Apgar score percentage*							
	1 min				*5 min*			
	Total recorded	*1-3*	*4-6*	*7-10*	*Total recorded*	*1-3*	*4-6*	*7-10*
Low	491	4.3	10.2	85.5	476	0.6	1.7	97.7
Mid	535	3.7	11.2	85.0	533	0.6	0.9	98.5
High	1066	4.2	7.3	88.5	1043	0.5	1.2	98.3
	2092				2052			

Table VI. Resuscitation, ventilatory support, NICU admissions*

	Physician group			
	Low (N = 491)	*Mid (N = 544)*	*High (N = 1071)*	χ^2 *(2 df)*
Need for resuscitation	65	106	86	5.4
NICU admission	110	90	78	4.2
Median length of stay (days)	10	10	11	$p = 0.29$
Requirement for ventilatory support	36	28	30	0.7
Median length of ventilator use (days)	2	8	4.5	$p = 0.12$

NICU, Neonatal intensive care unit.
*Combined vaginal and cesarean deliveries (cases per 1000 births).

Table VII. Neonatal morbidity and mortality

	Physician group			
	Low (N = 491)	*Mid (N = 544)*	*High (N = 1071)*	χ^2 *(2 df)*
Hypocalcemia Hyperbilirubinemia Hypoglycemia	75	79	63	1.8
Seizures	4	0	3	2.1
Respiratory distress syndrome	16	31	16	4.8
Wet lung	27	31	19	2.7
Meconium aspiration syndrome	6	4	8	1.2
Pneumonia or neonatal sepsis	16	29	19	2.7
Apnea	28	40	29	1.8
Intraventricular hemorrhage	2	7	4	1.9
Pneumothoraces	6	6	6	0.0
Deaths				
Neonatal	8	9	8	0.1
Fetal	4	0	3	2.0

*Combined vaginal and cesarean deliveries (cases per 1000 births).

they are acutely aware of past and pending claims against their partners.

The major legal threat to obstetricians is the allegation of failure to perform or delay in performance of cesarean sections. The infant's later cerebral palsy is attributed to asphyxia or trauma resulting from the alleged failures of the physician. The three major indicators—failure to progress, breech presentation,

and fetal distress—for primary cesarean section fall within this "legal risk" group.

Although all the physicians in our study have an equal awareness of the legal risks of delivering infants, it appears that the physicians with high cesarean rates are influenced by the risk to a greater degree than those with low rates. Their proportionate increase for all "legal risk" cesarean indications is supportive of this conclusion. Furthermore, two of the three physicians in our study who routinely obtain umbilical arterial blood gas studies on newborn infants are in the high cesarean rate group. This also suggests a higher sensitivity to legal risks since the sole purpose of routine performance of the test is the belief that it offers protection against liability claims. The authors do not share the latter belief.

The physicians with "high" cesarean rates in our study had substantially lower rates than those nationally reported (18% vs 25%) during the study period and lower than the physician with the lowest cesarean rate in the study by Goyert et al.[8] This occurred even though one of the two hospitals serves as a regional perinatal center. Therefore legal pressures were much more effectively resisted by these doctors than their national colleagues.[1]

With the waning of maternal morbidity in the early 1970s, the obstetric discipline concentrated on the reduction of newborn and infant morbidity. Considerable excitement ensued over the prospects of preventing intrapartum fetal "brain damage" and subsequent cerebral palsy. This resulted in a sharp increase in cesarean rates to protect the fetus from the "hostile" intrauterine environment or "traumatic delivery" with expected consequent prevention of newborn and infant neurologic impairment. Unfortunately, the anticipated benefits have not materialized. Cerebral palsy is neither prevented by appropriate obstetric response to asphyxial electronic fetal monitor patterns,[12] nor caused by a delayed response to similar changes.[13] Profound intrapartum asphyxia associated with many of 324 cases of umbilical cord prolapse did not increase the risk of later cerebral palsy in the infants who experienced that complication.[14] In recent findings related to acid-base status at birth and neurodevelopmental outcome at 4½ years, Dennis et al.[15] reported "the highest proportion of unimpaired children was found among those who were most severely acidotic at birth (pH 7.04; 2 below mean)." Cerebral palsy is not caused by prolonged labor, intrapartum asphyxia, or vaginal breech delivery[14, 16]; yet the obstetrician is blamed when it occurs in association with those conditions. This information has been available to the obstetric discipline since the publication by Nelson and Ellenberg[14] in 1984, entitled "Obstetric Complications as Risk Factors for Cerebral Palsy or Seizure Disorders." Among the population with cerebral palsy the following obstetric complications were not overrepresented: cord prolapse (0.3), fetal heart rate <100 beats/min (0.4), oxytocin augmentation (0.3), middle or high use of forceps (0.4), and second stage of labor longer than 59 minutes (0.3) compared with obstetric patients with no complications (0.3). The same authors reported no elevated risk for cerebral palsy when vaginal and cesarean breech deliveries were compared.[16]

We do not know, and the data from this study do not indicate, the optimal cesarean section rate. Quilligan[17] has suggested 8% and Porreco[3] has achieved a personal cesarean delivery rate of 6%. The combined rate for the two physicians with the lowest cesarean rates in our study was 7.8%. The neonatal outcome for these physicians is as good as that for the two physicians with high (19.6%) cesarean rates. Although our data do not conclusively identify an optimal cesarean section rate, the rate of the two lowest physicians is within the range suggested by Quilligan[17] and achieved by Porreco.[3]

Having identified the individual physician factor as a determinant of cesarean rate, we currently are identifying variations of patient management for the three major indicators of cesarean section—failure to progress, breech presentation, and presumed fetal distress. When physicians with high and low cesarean rates are compared for failure to progress, we are tabulating the following: parity, birth weight, gestational age, labor disorders, oxytocin dose, and duration for both induction and augmentation, use of intrauterine pressure catheter, cervical dilation at time of cesarean, use or nonuse of epidural anesthesia, trial of forceps or vacuum, variations in time of day (or night) of cesarean births plus all the individual patient characteristics analyzed in this article including neonatal outcome. Similarly, appropriate detailed analyses will be performed for breech and fetal distress cesarean births. The information obtained may be useful in the development of strategies to safely lower the cesarean rate.

Individual practice style is the only identifiable determinant of different cesarean rates for the 11 obstetricians in this study. In our opinion, the variation in individual rates is a result of the variation in physicians' reactions to current obstetric legal risks. Current cesarean rates can be substantially reduced without sacrificing fetal and newborn safety. This is unlikely to happen until medical-legal proceedings accord greater weight to sound scientific information.[11]

We thank the obstetric nurses at Bellin Memorial and St. Vincent Hospitals for their detailed record review and data collection; Vicki Sibilsky, our research assistant; and Professor David Jowett of the University of Wisconsin at Green Bay for his statistical analysis.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. STEPHEN A. MYERS, Chicago, Illinois. An increasing number of obstetricians agree with Drs. DeMott and Sandmire when they state that "current cesarean rates can be substantially reduced without sacrificing fetal and newborn safety." Congratulations are in order to those 11 obstetricians who were surveyed in this report and who, over the 3-year period in over 7000 deliveries, had only a collective cesarean rate of 14%. This is similar to the 11½ % cesarean section rate we reported last year for Mount Sinai Hospital Medical Center in Chicago, which has now been maintained for almost 4 years. As more studies are reported, we hopefully will be able to refine our understanding of indications for the procedure and perhaps curtail its performance when no benefit can be established for the operation. The Green Bay data demonstrate wide variations among individuals in determining route of delivery. The individual cesarean rates differed by a factor of 3, ranging from 6% to 20%. Wide personal variations in cesarean rates also prevail in hospitals with much higher overall rates. In such a context, the "physician factor" warrants scrutiny. However, instead of suggesting what may account for those differences, the authors have only tabulated them. Moreover, discussion of cerebral palsy and malpractice concerns, although possibly relevant to the issue, are not addressed.

The authors' working hypothesis is that individual physician factors account for variations in cesarean rates, not medical-obstetric differences in either populations or indications. Several recent publications already recognize this fact.[1, 2] These data merely repeat the same observation without any analysis as to why it is so.

Several methodologic concerns arise; there are errors in the tables. There are several examples of different numbers for the same data from table to table, i.e., Table II "high" primary rate = 11% compared with Table III "high" primary = 11.8%. Many such errors raise serious questions about accuracy and methodology of the data collection and analysis.) The low-mid-high groupings are entirely arbitrary, apparently to divide the 11 practitioners as equally as possible. However, within the low group the range is 5.6% to 11.8% (a factor of 2), whereas in the mid group the range is 12.7% to 13.8%, an unnoticeable difference. The outcome data refer only to Apgar scores. Moreover, twice as many low 1-minute scores are in the "low" cesarean group compared with the "high" cesarean group (4.3% [Apgar score of 1 to 6] versus 2.1%, $p < 0.05$). Too little analysis of this difference is made in this paper. One has to wonder whether such a restricted evaluation of outcome is adequate.

However, the basic question remains: *what* physician factors account for individual differences in cesarean rates? To answer this important question, others have to be asked and answered. For example: (1) How many patients have had more than one previous cesarean section? How many of these were allowed a trial of labor? (2) What are the individuals' vaginal birth rates after previous cesareans sections? What are their vaginal breech delivery rates? (3) What are the average birth weights of infants delivered by cesarean section for dystocia? What proportion have birth weights <3000 gm? (4) How often is conduction anesthesia or oxytocin used?

Similarly, a more direct assessment of individual malpractice perception and experience could support the authors' proposition that "the variation in individual rates is a result of the variation in physicians' reactions to obstetric legal risks." The following questions are

raised. (1) Which of the 11 physicians were sued? What were the allegations? (2) Would route of delivery have made a difference? (3) Was the suit settled or did it proceed to jury award? (4) Were adverse outcomes experienced in the absence of legal action? (5) Did any case of cerebral palsy occur during this study?

That individual perceptions can influence cesarean section rates is, in fact, quite well demonstrated by these data. With a collective cesarean rate of 14%, a lower cesarean rate was observed in infants weighing more than 4500 gm than in infants weighing <1500 gm (53 of 81 >4500 gm vs 34 of 41 <1500 gm; $\chi^2 = 4.14$; $p < 0.05$). An understanding of factors accounting for such observations, whether in Green Bay or Chicago, would serve our patients and our profession well.

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Dr. Robert E. Wall, Denver, Colorado. The authors have provided a retrospective review of all singleton cesarean deliveries performed by 11 board-certified obstetricians from 1986 through 1988. Their stated objectives were: (1) to examine factors that influence route of delivery decisions and (2) to examine the effect of the delivery route on maternal and newborn outcomes.

In their study design the authors compared all cesarean deliveries with the next single vaginal delivery for a given practitioner following each of the index cesarean deliveries. Arbitrarily, all cesarean deliveries for multiple gestations were excluded from the cesarean group without eliminating the corresponding vaginal delivery from the vaginal delivery group. Although not an optimal design, the impact on their results was probably small.

The 11 physicians were divided into three study groups based on cesarean delivery rate. What factors determined how many physician groups were compared? Why was physician no. 4, whose cesarean rate was 11.8%, included in the low cesarean rate group with physician no. 1, whose cesarean rate was only 5.6%? Furthermore, why was physician no. 5, whose rate was 12.7%, included in the middle cesarean rate group, rather than with physician no. 4 at 11.8%? The rationale behind the construction of these physician groups remains unclear.

In determining the results, only *scheduled* repeat cesarean deliveries were included in the *repeat* cesarean rate. Patients who underwent a second cesarean delivery, despite a trial of labor, were included in the *primary* cesarean group. Although many obstetricians now allow a trial of labor, some are unwilling to use interventions such as epidural anesthesia, oxytocin augmentation, or induction of labor that will allow maximum chance for successful vaginal births after cesarean section. They frequently "bail out" early in labor without an adequate trial. Should we also include these so called vaginal births after cesarean section failures as primary cesareans?

In their results the authors also stated, "Our data clearly demonstrate no difference in the condition of newborn infants . . . comparing low to high rate physician groups." However, comparison of neonatal outcome between the low and high cesarean rate physician groups included only (1) Apgar scores, (2) the need for neonatal resuscitation, and (3) admission to and length of stay in the neonatal intensive care unit. Umbilical artery blood gas determination, neonatal sepsis, intraventricular hemorrhage, apnea and bradycardia in the nursery, neonatal seizure activity, neonatal mortality, and later childhood developmental delays were not or could not be compared between low and high cesarean rate physician groups. Without additional data, I do not believe the authors can claim to "clearly demonstrate no difference in the condition of newborn infants . . . comparing low to high cesarean rate physician groups."

The incidence of maternal complications reported was low in both vaginal delivery and cesarean delivery groups. It is not possible to determine the numbers of each maternal complication reported, nor their distribution among physician groups. The authors reported an incidence of postcesarean endometritis of <1.8%. What was their definition of endometritis?

Given the very low incidence of individual complications in each physician group, were there really "no statistically significant differences in the rates of these complications among physician groups"? The authors should subject their evaluation to statistical power analysis to be certain their conclusion is valid. Would other parameters indicative of maternal outcome, such as wound infection rate, length of hospital stay, and cost of hospitalization, provide additional comparisons between low and high rate physician groups?

The authors compared the morbidity of *all* newborns and mothers delivered by cesarean sections with *all* those delivered vaginally, regardless of physician group. However, no rational comparisons can be made based solely on route of delivery. Preexisting maternal and fetal compromise themselves are often the major determinants of delivery route.

Finally, the authors concluded that "the major determinant of route of delivery is the individual practice style of each physician." I generally agree with this assessment. However, they further stated, "the variation in individual rates is a result of the variation in physicians' reactions to current obstetric legal risks." They provided no data regarding other very important intrapartum practice styles that could explain the marked variation in individual cesarean rates. These variables include (1) the use of intrauterine pressure monitoring

to adequately document "failure to progress," (2) the use of external cephalic version to avoid cesarean breech delivery, (3) the use of fetal scalp pH determination or intraamniotic saline solution infusion to evaluate and treat "fetal distress," and (4) the use of epidural and caudal anesthesia in labor, and its effect on the progress of labor. Could variations in any or all of these factors also explain the marked variation in cesarean rates between individual physicians?

In summary, the authors and the entire physician group are to be commended for maintaining a cesarean rate well below the national average in the United States. Their mothers and newborn infants appear to have very low rates of complications after both vaginal and cesarean delivery. I agree that the fear of litigation has an effect on individual practice style. However, this study does not provide us with the data necessary to quantitate the role of current obstetric legal risks on a physician's individual practice style or cesarean rate. The authors omitted multiple variables that, in my opinion, substantially influence decisions concerning the route of delivery. The data presented are inadequate to accurately compare maternal and newborn outcomes between the low and high cesarean rate physician groups. If additional information can be supplied and if further analysis is conducted, I believe this study will be able to provide us with information regarding the impact of "fear of litigation" on an individual physician's cesarean rate. Any discrepancy in maternal and newborn outcome between the cesarean rate physician groups may then be evident. Finally, I would also be interested in knowing the individual cesarean rates of the authors during this study period.

Dr. Murray J. Casey, Omaha, Nebraska. Dr. Sandmire told me about this article a few weeks ago, so I have had a chance to think about it a while; although he did not tell me the specifics and I have not read it. I hope that Dr. Wall's unanswered questions are answered, but in thinking about the authors' findings, it gave me an opportunity to try to combine this with some of the other things that I know.

For many years researchers in business and management behavior have recognized that although there is a continuum of risk and risk avoidance characteristics in personality, to some extent this can be stratified. Researchers do not know how to deal with the categorization once it is defined. For instance, there seem to be no quantifiable factors that would predict who would be a better manager in a mature or in an emerging firm or who would be a better entrepreneur, etc. So the problem of who will react to certain agreed obstetric data by performing a cesarean section may reflect much more basic levels of individual personality than simply the fear of litigation.

Dr. Richard A. Hartman, St. Louis, Missouri. I have only one question. Did the individual workload of any one physician affect the cesarean rate? I think physician No. 1 had a total of about 500 deliveries. Physician No. 10 had almost 1200 in a 3-year time period.

Dr. Sidney F. Bottoms, Detroit, Michigan. I would like to compliment the authors. I recognize that there are many questions you can ask about a study in this area; however, it is literally impossible to study everything about labor and delivery all at once.

I think it is important to stop fooling ourselves and saying "Oh, well there might be some difference between these patients if you studied everything on God's earth and we start to deal with the issue because everybody who's had any experience in the delivery room knows that some people are going to go to the knife a whole lot faster than the others." I don't know anyone who would deny that.

If you think about your own day-to-day observations, you know that some doctors' patients are always more apt to have a cesarean section. I compliment the authors' forthrightness to start dealing with an important issue.

Dr. Jack W. Pearson, Tucson, Arizona. A few years ago I reported from Indiana University a 9-year experience on obstetric outcome in an indigent urban population with reference to cesarean section rate and associated perinatal mortality rate.[1] At that time we were challenging the belief that the increasing cesarean section rate was the cause of the decreasing perinatal mortality rate.

Our cesarean section rate over that period remained stable and remarkably close to what was reported today at the lower end of the spectrum: approximately an 8% *total* cesarean section rate. Over 3000 deliveries a year and a total of approximately 30,000 deliveries were analyzed.

During that same time, the perinatal mortality rate decreased 50%. On the basis of our findings, I would suggest that our improvement of perinatal outcome over the past 10 to 20 years may relate to the performance of cesarean section and other aspects of improved obstetric care. However, our experience would suggest that dramatic improvements in neonatal care have been a far more significant influence on our improving perinatal outcome.

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Dr. Paul C. Nehra, Detroit, Michigan. In some hospitals, especially community hospitals, there is an active family practice service, and family practitioners tend to refer patients to certain obstetricians more often than others. That may lead to a higher cesarean section rate for certain physicians in these community hospitals. I

do not think this has been addressed in any of the previous studies.

Did some of the physicians in this study have higher cesarean section rates potentially because they were the chosen referral physician?

Dr. Sandmire (Closing). The distribution of the groups was somewhat arbitrary. I do not think we could have distributed the data to satisfy everyone, but we did the distribution to have larger groups for statistical analysis. In other words, the morbidity is rather infrequent. We thought that instead of calculating morbidity and outcome measures for each individual obstetrician, we should use groups to give greater statistical power. We agree with the discussants that there is little difference in cesarean rates for the last physician in the low group and the first physician in the middle group. The same is true for the last and first physicians in groups two and three, respectively. Because our conclusions are based on outcomes comparing the low and high cesarean rate physician groups (where there is a substantial difference [9.8% vs 18.0%]), our groupings are appropriate.

Dr. Wall mentioned that we did not use enough different measures of outcomes to compare one group with the other. We did send multiple updated papers to the discussants; I hope he got the more recent ones. Although we did not include it on the tables, we did analyze all of the many different outcomes, including seizures in the newborn, sepsis, length of respirator use, and neonatal intensive care unit admissions and length of stay. He also mentioned the difference in Apgar scores between the high and low cesarean rate groups. We apologize that there was an error on Table V in an earlier draft. The corrected table demonstrates no difference in Apgar scores between the different physician groups.

With regard to the request for more information, this is our first study with this patient population. We will be providing at least three more articles, each reporting on a detailed analysis for the major indications for cesarean section. For example, in the failure to progress group, we will report the length of labor, the latent period, and the degree of cervical dilatation at the time of intervention by cesarean. In addition, the oxytocin dose and duration of use will be reported. The influence of birth weight on cesarean rate will be analyzed as well as use or nonuse of epidural anesthesia. We will provide all the information that was suggested. As Dr. Bottoms says, you can't deal with everything in a 12-minute paper or one article.

We have a relatively small community and every obstetrician has equal knowledge about the legal risks involved in practicing obstetrics. That will not be influenced by who was sued and who was not; practically speaking, almost all the physicians in the study group have been sued, some more than others; but for those few young physicians who have not, I tell them to be patient.

I think I commented on most of the things that Dr. Myers asked about.

There were some important questions by Dr. Wall regarding intrauterine pressure catheter use or nonuse, epidural anesthesia, cephalic version, breech presentation, and scalp pH. Those questions will be answered in our future articles, but I can tell you that epidural anesthesia is not used and that the intrauterine pressure monitor was used very infrequently. Those were not variables that differed from one obstetrician or group of obstetricians compared with the others.

Dr. Hartman asked if the individual physician workload affected the cesarean rate. Dr. DeMott, who is physician No. 1 in Table I, came to Green Bay about halfway through the study period and had only 408 deliveries. Obstetrician No. 8 was also present for only the last half of the study period. The reason we grouped the physicians is because 408 deliveries is not an adequate sample size. I am No. 4 on the table.

There was a comment that the data do not prove that it is as safe for the infants who are delivered by physicians with low cesarean rates. We believe that our data *do* demonstrate equal neonatal outcomes for physicians with both low and high cesarean rate. In addition, I think that obstetricians have worked themselves "into a hole" in which the burden of proof somehow has fallen on advocates of fewer operative deliveries, when in fact those who contend higher cesarean rates improve outcome are the ones who should have to present justifying data.

Dr. Nehra asked about family practice referrals. I do not believe that is a factor in cesarean rates because the physicians are grouped by cesarean rate rather than professional associations. In fact, physicians in the high group represent three different practices.

Our conclusion that medical-legal risks influence cesarean rates is somewhat inferential and based on the personal knowledge that we all make some decisions based on those risks. In addition, no other variable explaining different cesarean rates was identified.

We have not used the term *unnecessary* cesarean section. Every one of these cesarean sections was necessary. The obstetrician performing each cesarean had a reason to perform the cesarean. We are saying that perhaps some of those reasons for performing cesarean sections were not totally appropriate from the scientific standpoint but arise from legal pressure. If we are to solve a problem, then we have to be sure we know what the problem is; and I believe the cesarean section rate is higher than optimum, and I think the major contributor to that problem the legal pressure to which our discipline is subjected.

Randomized prospective trial comparing ultrasonography and pelvic examination for preterm labor surveillance

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This study was designed to compare the effectiveness of cervical assessment by either ultrasonography or bimanual pelvic examination in a program for preterm labor surveillance. Patients ($n = 57$) at risk for preterm birth were seen once a week for patient education, review of symptoms, and cervical evaluation. Cervical evaluation was assigned randomly to either ultrasonographic evaluation or pelvic examination. The groups did not differ in demographic or obstetric factors. The overall rate of prematurity was 18%. Preterm labor was more frequent with ultrasonographic evaluation (52%) than with pelvic examination (25%) ($p < 0.05$). The group evaluated by ultrasonography received oral tocolytic agents (55%) more than the group that had pelvic examinations (21%) ($p < 0.02$). The groups did not differ in infant birth weights, length of gestation, or neonatal mortality or morbidity. In this prospective randomized study of patients at risk for preterm birth, patients under surveillance by ultrasonographic assessment of the cervix did not fare better than those assigned to bimanual examination. (Am J Obstet Gynecol 1990;162:1603-10.)

Key words: Preterm birth prevention, ultrasonography, precocious cervical maturation, prematurity

Preterm birth remains a leading cause of infant mortality and morbidity in this country. Efforts to lower the rate of preterm birth have been successful with a combination of professional and lay education, risk assessment, patient education regarding warning signs of labor, and recommendations for limitation of physical activity,[1] close surveillance, and intervention for early preterm labor.[2] Although the physiology of the onset of normal and preterm labor is not well understood, there is considerable evidence that active preterm labor is often preceded by a period of increasing uterine activity and associated change in the cervix that may be relatively asymptomatic.

Assessment of the cervix, either in all prenatal patients, or in a subset of patients at increased risk, is an integral part of all programs for prevention of preterm birth. Bouyer et al.[3] identified precocious maturation of the cervix on physical examination as the strongest single risk factor for preterm birth in 7937 pregnancies. Herron et al.[2] reduced the rate of preterm birth in a program of risk assessment and targeted intense patient education, surveillance, and weekly bimanual pelvic examination. Papiernik et al.[4] advocated pelvic examination of all prenatal patients at each visit. Stubbs et al.[5] suggested that pelvic examination at 28 weeks in all pregnancies may reduce the incidence of preterm birth by identifying asymptomatic patients with preterm abnormal cervical change. Bouyer et al.[3] reported the normal range of pelvic examination for each gestational age, and the ability to predict risk of preterm birth on the basis of a single examination.

As ultrasonographic equipment and techniques have improved, imaging of the cervix and lower uterine segment has been recommended,[6] but there are technical difficulties.[7] O'Leary and Ferrell[8] described good correlation between the Bishop score on bimanual examination and an ultrasonographic score in 46 patients. Brown et al.[9] also demonstrated good correlation between digital examination and both transabdominal and transvaginal ultrasonography in 20 unselected patients. Ayers et al.[10] used ultrasonography in 88 patients with previous second-trimester losses and believed its use was beneficial. There has been no prospective study comparing ultrasonographic evaluation and bimanual assessment of the cervix for preterm birth prevention.

The purpose of this study was to compare in a prospective randomized fashion the effectiveness of cervical assessment by either ultrasonography or bimanual pelvic examination in a program for preterm labor surveillance.

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Material and methods

Pregnant women of less than 34 weeks' gestation who were at risk for preterm birth were assessed by a risk scoring system.[11] Patients with a risk score of 10 or greater were offered participation in this study. Patients were excluded from entry into the study if they had already been treated for preterm labor during the current pregnancy with intravenous tocolytic agents, oral tocolytics, or emergency cerclage. This study was approved by the institutional human investigation committee and written informed consent was obtained.

Patients planning to be delivered of their infants at William Beaumont Hospital in Royal Oak, Michigan were enrolled in the study between July 1, 1985, and Aug. 31, 1988.

Patients were seen weekly at the hospital by one of the authors from 20 weeks' gestation (or at entry if enrolled after 20 weeks) until 37 weeks' gestation for patient education, review of symptoms, and cervical evaluation. Each patient education and symptom review visit was done by one of the authors and lasted 30 to 60 minutes. Routine prenatal care was continued by the primary physician, who was also responsible for intervention if surveillance demonstrated significant changes.

Patients were assigned by the use of random number table at the time of entry to a method for weekly cervical evaluation, either by bimanual pelvic examination ("pelvic group") or by transabdominal ultrasonographic examination ("ultrasonography group"). This cervical evaluation was done weekly in all patients. Patients assigned to the ultrasonography group who reported a change in symptoms consistent with increased uterine activity at the weekly surveillance visit would also undergo pelvic examination.

For ultrasonographic examination of the cervix, a sector transducer of a GE RT3000 (Milwaukee) or Acuson (Mountain View, Calif.) ultrasonographic scanner was used to measure cervical length in the supine position. The superior wall of the bladder was always perpendicular to the cephalocaudad axis to ensure an accurate, standardized study. If the bladder was too full, cervical length was falsely elongated; if it was not full enough, the length could not be measured. The length was measured from the internal os to the external os in the sagittal plane with the transabdominal approach. Visualization of the cervical canal was a requirement for measurement and reporting cervical length. The internal os is usually identified by a dimple in the uterine contour. If the dimple was not visualized, a line extending through the canal was extended to the interior uterine contour. If the external os was not visualized, the measurement was taken at the end of the visualized cervical canal. A significant change was identified if the cervix was shorter by ≥ 1 cm than the previous examination. This distance was chosen because there was often <1 cm of variation between examinations. Funneling of the cervix was noted but not considered abnormal unless other findings (e.g., shortening of the canal) were also observed. Dilatation of the canal was considered significant.

Patients were asked to increase fluid intake and not void before the study and then were asked to partially empty their bladders if the standard bladder image could not be obtained. Patients assigned to the ultrasonography group underwent a basic full study at the first visit (biparietal diameter and femur length[12]). Subsequent visits for assessment of the cervix were brief (5 to 10 minutes including adjustment of bladder volume).

The pelvic examination group had a bimanual examination and a modified Bishop score[13] weekly by one of the authors. Softening of the cervix from 34 to 37 weeks' gestation was considered normal; any other change in the Bishop score was considered significant.

The primary obstetrician was notified immediately if the ultrasonographic surveillance or pelvic examination showed a significant change.

Shortly after the study began, home ambulatory uterine monitoring became available and all patients enrolled thereafter underwent home monitoring (Tokos Medical Corp., Santa Ana, Calif.). When evidence of possible labor was identified during a weekly study visit (change on ultrasonographic evaluation or pelvic examination, marked increase in patient symptoms), the primary obstetrician was contacted by telephone for further management. This research study did not dictate or recommend further management. Further observations by standard tokodynamometry required hospital admission at our institution.

For purposes of this study, a patient was identified retrospectively as having preterm labor if she had any of the following before 37 completed weeks of gestation: (1) uterine contractions and progressive cervical dilatation resulting in preterm birth, or (2) frequent uterine contractions that were treated with hospitalization and initiation of or an increase in pharmacologic therapy, or (3) precocious cervical maturation that was treated with hospitalization and initiation of or an increase in pharmacologic therapy.

Patients with multiple gestations were enrolled in this study, randomized in the above described system, but will be reported separately.

Clinical characteristics of the two groups were analyzed by t test, χ^2 and Fisher's exact tests as appropriate. Survival analysis was used to compare the primary outcome measure, gestational age at delivery, between the two groups.[14] A value of $p \leq 0.05$ was considered significant.

Table I. Demographic and obstetric history by assigned group

	Method of surveillance		
	Pelvic examination	*Ultrasonography*	*Significance*
No. of patients	28	29	
Maternal age (yr, mean ± SD)	29.4 ± 4.5	27.0 ± 5.1	NS ($p < 0.06$)
Race, white, *n* (%)	28 (100%)	28 (97%)	NS*
Gravidity (mean ± SD)	3.9 ± 1.7	3.2 ± 1.8	NS
Previous term birth (mean ± SD)	0.4 ± 0.7	0.3 ± 0.6	NS
Previous preterm birth (mean ± SD)	1.1 ± 0.5	1.1 ± 0.8	NS
Abortions (mean ± SD)	1.4 ± 1.4	0.9 ± 1.4	NS
Living children (mean ± SD)	1.1 ± 0.7	1.0 ± 0.9	NS
Risk score (mean ± SD)	17.3 ± 6.8	20.8 ± 9.9	NS
Patient source, clinic, *n* (%)	8 (29%)	14 (48%)	NS

*Fisher's exact test (two-tailed).

Results

Fifty-nine patients with singleton pregnancies were enrolled. Two patients were removed from the study because they were delivered prematurely for unrelated reasons (severe intrauterine growth retardation at 34 weeks' gestation, abnormal fetal testing at 32 weeks' gestation in type I diabetes mellitus). The groups did not differ in number of previous preterm or term births, previous abortions, race, preterm risk score, primary physician source (private versus clinic), or use of home monitoring (Table I). There appeared to be a trend for the pelvic group to have an older maternal age than the ultrasonography group ($p < 0.06$). Management was not significantly different (Table II) with regard to the following: use of cerclage, intravenous tocolytic agents, use of betamethasone, number of predelivery admissions, or number of days in the hospital before delivery. The ultrasonography group did receive oral tocolytic agents more frequently ($p < 0.02$) than the pelvic group.

Dilatation of the cervical canal was not seen on ultrasonography without significant shortening of the length of the canal.

Pregnancy outcome in the two groups is shown in Table III. The overall rate of preterm delivery (<37 weeks' gestation) was 18%. The overall rate of preterm labor was 39%. Preterm labor was more frequent in the ultrasonography group (52%) than in the pelvic group (25%) ($p < 0.05$).

Life-table analysis of gestational age at delivery demonstrated a significant difference ($p < 0.05$).[15] No significant difference was found when all deliveries after 37 weeks' gestation were grouped as term deliveries (i.e., results censored after 37 weeks.)[16] Thus the primary difference between the groups was accounted for by the differences beyond 37 weeks' gestation.

Power analysis[17] indicated that this study had an 80% chance of detecting a 2.5-week prolongation of gestational age in the ultrasonography group at a value of $p < 0.05$.

Birth weights were similar in both groups, as were Apgar scores, neonatal hospital days, sepsis (none in either group), sex distribution, and neonatal complications. One newborn in each group died (infants with birth weights of 500 and 375 gm).

Because multiple outcome variables were studied without any observed benefit, the actual power of this study to identify a favorable benefit to ultrasonography is probably higher than 80%.

Comment

In this prospective randomized study of patients at risk for preterm birth who were followed in a program of preterm labor surveillance, patients followed by weekly ultrasonographic assessment of the cervix fared no better than those followed by weekly bimanual examination. The ultrasonography group had more cases of preterm labor ($p < 0.05$).

This is the first randomized prospective study comparing these two methods of assessment of the cervix, and demonstrates no apparent benefit to ultrasonographic surveillance. This finding differs from the observation of others.[10, 18]

Theoretically, ultrasonographic assessment of the cervix by transabdominal scanning has the advantages of less risk of ascending transvaginal infection, less risk of local prostaglandin release that is associated with bimanual examinations (Ferguson reflex), and better assessment of the internal os. Conversely, a bimanual examination with a Bishop score assesses factors that ultrasonography does not: consistency of the cervix, location in the vagina, and station of the presenting part.

The apparent difference in rates of preterm labor

Table II. Management of pregnancy by assigned group

	Method of surveillance		
	Pelvic examination (n = 28)	*Ultrasonography (n = 29)*	*Significance*
Gestational age at entry (wk, mean ± SD)	21.5 ± 2.2	21.6 ± 2.8	NS
Cerclage, *n* (%)	8 (29%)	8 (26%)	NS
Ambulatory tokodynamometry, *n* (%)	25 (89%)	24 (83%)	NS
Tocolysis			
Intravenous, *n* (%)	6 (21%)	9 (31%)	NS
Oral, *n* (%)	6 (21%)	16 (55%)	$p<0.02$
Betamethasone, *n* (%)	3 (11%)	6 (21%)	NS
Hospitalization before delivery			
No. of admissions (mean ± SD)	1.1 ± 1.5	1.1 ± 1.5	NS
No. of days (mean ± SD)	2.3 ± 3.5	8.1 ± 17.5*	NS ($p<0.1$)
Patients admitted, *n* (%)	17 (61%)	18 (62%)	NS

*Includes one admission of 84 days.

Table III. Pregnancy outcome by assigned group

	Method of surveillance		
	Pelvic examination (n = 28)	*Ultrasonography (n = 29)*	*Significance*
Preterm labor, *n* (%)	7 (25%)	15 (52%)	$p<0.05$
Delivery at 37 wk, *n* (%)	3 (11%)	7 (24%)	NS*
Gestational age at delivery (mean ± SD)	38.3 ± 3.3	36.9 ± 4.1	NS
Neonatal deaths, *n* (%)	1 (4%)	1 (3%)	NS†
Birth weight (gm, mean ± SD)	3154 ± 713	3016 ± 904	NS
Apgar score (mean ± SD)			
1 min	7.5 ± 1.6	7.3 ± 1.7	NS
5 min	8.6 ± 1.5	8.5 ± 1.5	NS
Fetal distress in labor, *n* (%)	1 (4%)	3 (10%)	NS†
Female sex, *n* (%)	16 (57%)	14 (48%)	NS
Cesarean section, *n* (%)	8 (29%)	13 (45%)	NS
NICU admission, *n* (%)	5 (18%)	9 (31%)	NS
Hospital days (mean ± SD)			
Newborn	3.0 ± 1.5	3.9 ± 3.3	NS
Mother, post partum	2.8 ± 1.3	3.3 ± 1.6	NS

NICU, Neonatal intensive care unit.
*Fisher's exact test (one-tailed).
†Fisher's exact test (two-tailed).

and use of oral tocolytic therapy in these comparable groups is unexplained. Possible explanations are: (1) The groups differ in some unidentified risk factor for preterm labor; (2) a chance observation that occurred randomly when in fact there is no difference (this explanation has a 4% probability); (3) ultrasonography provides a less effective tool for early intervention for treatment of cervical change; (4) ultrasonographic surveillance predisposes to preterm labor in some way. Of possible relevance to the latter is the clinical observation that bladder distention may increase uterine activity. Studies are currently underway that try to address these issues.

The precocious maturation of the cervix is a significant risk factor for preterm birth, the importance of which cannot be overstated. In a random examination during pregnancy by either ultrasonography or pelvic examination, such a finding warrants further evaluation. In a program of preterm birth prevention including weekly examination of the cervix, this study

demonstrates no advantage, and possible problems, with surveillance by ultrasonography rather than bimanual examination.

We acknowledge the contribution by Tokos Medical Corporation in providing home ambulatory tokodynamometry services.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. RICK W. MARTIN, Jackson, Mississippi. The authors have evaluated the usefulness of ultrasonographic assessment of the cervix in the management of pregnant women at risk for preterm labor. Cervical dilatation has been observed to be a reliable predictor of preterm delivery as a component of formal prematurity prevention programs.[1] Cervical dilatation has been determined by ultrasonographic evaluation. Therefore it is reasonable, to determine the benefit from cervical evaluation by ultrasonography compared with bimanual examination. This is not the first article to deal with this modality, however it is the first to study its benefit in a randomized, prospective manner. Ultrasonography does allow evaluation of the internal cervical os when access is limited with the bimanual examination. Although difficulties, primarily concerning interpretation and the effects of bladder filling on cervical length have been reported, O'Leary and Ferrell[2] have shown correlation between an ultrasonographic cervical scoring system and the Bishop score. Transvaginal ultrasonography has been reported to offer slightly better imaging of the cervix than the abdominal approach.[3] This method would be particularly useful in the obese gravid woman. I would be interested in difficulties the authors encountered with the ultrasonographic examination. What factors affected the reliability of ultrasonographic measurement?

Table III indicates a significant difference in the number of women in each group who had preterm labor. This would not be expected since the groups were chosen at random. Although a standard risk scoring method was used to select participants, the individual risk factors of the two groups may have been different. For instance, we have found that two or more previous preterm deliveries carries a 2.5-fold greater risk (70%) than one previous preterm infant (30%). Alternatively, the diagnosis of actual preterm labor may have been incorrect. Table II indicates a greater number of women were treated with oral tocolytic agents in one group even though approximately equal numbers of women were treated with parenteral drugs. This may indicate that uterine irritability without cervical change was treated as preterm labor. Would the authors comment on the criteria for diagnosis and treatment of preterm labor in this study?

Not only were the capabilities of ultrasonography tested in this study, but there was an opportunity to determine the effect of bimanual examination on the occurrence of preterm labor and premature rupture of membranes. Although several studies have shown no adverse effects of weekly cervical examinations in preterm gestations, there is at least one study in term pregnancies indicating a greater incidence of premature rupture of the membranes in women who receive regular pelvic examinations than in those in whom the routine examination is omitted.[4] In this article no statistical difference was found between the two groups, suggesting no effect. This is reassuring to those of us who use pelvic examinations in patients at risk for pre-

term delivery. The incidence of premature rupture of the membranes in this study is not reported; this is a factor that might be important in women at risk for preterm delivery. To study the question of cervical manipulation and preterm delivery, it is also necessary to exclude patients who have had extensive manipulation with a cerclage procedure. These patients comprised a large proportion of the authors' study group. If patients undergoing cerclage are excluded, does weekly cervical examination influence the outcome?

Despite the negative findings of the study, a sufficient number of patients were included to reach the conclusion that weekly ultrasonographic examination of the cervix offers no benefit over current standard practice. The findings support our clinical experience. A cost analysis of such a program of ultrasonographic examination would also support the current approach of routine bimanual examination.

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DR. KENNETH J. LEVENO, Dallas, Texas. Early identification of pregnancies at risk for preterm birth is currently receiving major emphasis since prevention is preferable to active treatment of preterm labor. Although women with prior preterm births are clearly at risk for recurrence, there is increasing interest, as evidenced by the authors' report, in other risk factors, such as asymptomatic cervical effacement and dilatation after midpregnancy.

Interestingly, "premature" cervical change as a risk factor for preterm birth is a relatively recent observation. Until this decade conventional obstetric teaching has held that asymptomatic preterm cervical dilatation is a normal anatomic variant, especially in parous women.

Between 1961 and 1969 five investigations on the significance of early third-trimester cervical dilatation were published. In three reports it was observed that such cervical change was not linked to preterm birth,[1-3] whereas an association was found in the other two studies.[4,5] During the next decade identification of pregnancies at risk by means of scoring systems based on socioeconomic status, reproductive history, daily habits, and current pregnancy complications received impetus as a result of pioneering work by Papiernik and Kaminski[6] and Creasy et al.[7] Preterm cervical dilatation was a risk factor in both scoring systems. At least three reports on precocious cervical dilatation were published during the 1980s and have confirmed this clinical finding as a harbinger of preterm birth.[8-10] Therefore I believe we must conclude that early third-trimester cervical dilatation is meaningful in predicting the risk of preterm labor. Unfortunately, detection of such cervical change has required manual examination, which may have unwanted consequences. Specifically, manual examination of the cervix at term has been reported to triple the frequency of membrane rupture before labor.[11] The recent development of high-resolution ultrasonographic technology that permits cervical imaging as now described by the authors inevitably is an attractive alternative to manual examination of the cervix.

Dr. Lorenz and colleagues designed their study to compare the effectiveness of cervical assessment by ultrasonography with manual pelvic examination in the prevention of preterm labor and found no advantage for ultrasonographic evaluation. This is the first reported randomized investigation with this goal. Actually, this investigation is based on the somewhat novel concept that ultrasonographic examination may itself be a therapeutic intervention rather than simply a diagnostic modality. Whether use of ultrasonography is "therapeutic" is an important and timely subject given the widespread application of obstetric utlrasonography, arguably without proof of benefit. Indeed, ultrasonography could be construed to be harmful on the basis of this investigation because preterm labor occured twice as often in the ultrasonography group. Alternatively, we can also conclude that manual examination of the cervix is not harmful.

I have two primary criticisms of this investigation. First, given the several vagaries involved in the diagnosis and management of preterm labor, I suspect that the sample size used may be too small to judge the efficacy of ultrasonography as a "therapeutic" intervention. For example, most investigations that concern the interventional merits of ultrasonography include hundreds and even thousands of pregnancies. Second, I am not convinced that sufficient experience with cervical ultrasonography has been published so that we can firmly conclude that it is as useful as manual examination in assessing either cervical condition or risk of preterm labor. The authors' study may have the perfect design necessary to address these roles of cervical ultrasonographic imaging compared with manual examination. Therefore I suggest an analysis of the data presented to answer the question, "How does cervical ultrasonography compare with manual examination in the *prediction, not prevention,* of preterm labor?" I think this information would be particularly useful since avoidance of cervical manipulation in pregnancies at risk for preterm labor could potentially be very important.

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DR. STEPHEN L. BLOOM, Waterloo, Iowa. My question is not directly related to the purpose of the article. How do you treat women with cervical effacement, dilatation of the cervix, or both, in the last 4 months of pregnancy when there is no evidence of uterine contractility?

DR. RUDI ANSBACHER, Ann Arbor, Michigan. I have one question. Do you think if you had done this study with an indigent population whose members were socioeconomically deprived, you would have found different results?

DR. JOHN A. GARBACIAK, JR., Phoenix, Arizona. I would like Dr. Lorenz to comment on the bladder manipulation that was necessary for the weekly ultrasonographic examination—was this potentially an irritating factor causing uterine irritability or what he defined as preterm labor?

DR. EDUARD EICHNER, Cleveland, Ohio. I want to go back years again as a historian. I did work with relaxin to stop labor 40 or 50 years ago when some groups used relaxin to examine a softened cervix and to make it soft. Vaginal examination helped produce labor in some women by pushing the finger through the cervix so soft that it would admit it.

We started with our original group of women with ruptured membranes suspected as the cause of labor, and we were the first to report that ruptured membranes by themselves did *not* produce labor unless the pregnancy was close to term. The ratio was reversed the longer from true term gestation, with less likelihood of labor production.

The only question involved is the question of the vaginal examination. Do you just examine or do you do some manipulation?

We lost pregnancies in our patients with premature rupture of membranes very far from term because of amnionitis that developed because of ruptured membranes. We were able to show that ruptured membranes per se did not produce labor except at term.

We used relaxin, which softened the cervix. If there was no sexual activity involved and no other manipulation except the pelvic examination, the examination itself did not produce labor.

DR. L. RUSSELL MALINAK, Houston, Texas. Given the variability of the anatomy of the external cervical os as a result of distortion from previous lacerations, large nabothian cysts, or other factors, is that site an optimum end point for measuring the length of the cervical canal?

DR. LORENZ (Closing). I would like to thank all the discussants for very cogent comments. I will begin with Dr. Martin's comments. He questioned what the difficulties were with the ultrasonography technique. Certainly I would agree with everything that has been said about the problems with bladder volume. I refer to an excellent paper by Confino et al.[1] in 1986 that listed bladder volume as one of the pitfalls of ultrasonographic evaluation of the cervix.

The second problem we found very frequently after about 32 weeks' gestation. If the presenting part was relatively low in the pelvis, then evaluation of the cervix was virtually impossible.

The comments about criteria for diagnosis of preterm labor are extremely relevant and may explain our findings. The research team was working on surveillance of the patients who were asymptomatic. That included weekly visits with either method that we described, as well as patient education. If a finding of change on ultrasonography was noted, which we defined as a change of at least 1 cm shortening in length, then the attending physician was notified. The diagnosis of preterm labor and the management was the responsibility of the clinical team.

Most patients were private patients and remained under the care of their attending physicians. Just as there are considerable differences of opinion on the national basis regarding treatment for uterine irritability, uterine contractions, etc. this was the case in our institution. There were not many physicians involved, and the randomization was an attempt to try to control for this aspect. However, the basis of this study was the impact on the "bottom line" of the preterm delivery rate, and the preterm delivery rate did not appear to be different.

The question about risk scoring is also important. In the Creasy system 10 points, the maximum value, are allotted for a single preterm birth, and the number of preterm births was multiplied by 10. A patient with two previous preterm births would have double the risks, and so on. The rates of previous preterm births in the two groups were equal. Similarly, the risk scoring with the Creasy method was the same; thus I think the groups were similar from the standpoint of risk based on previous obstetric history.

The point about premature rupture of membranes was quite pertinent. We saw only two women with preterm premature rupture of membranes, and both patients had ultrasonographic evaluation. Similarly, the latent phase from the onset of ruptured membranes until delivery for the whole population was no different between the two groups. We analyzed these patients without the cerclage group, and our findings remained the same: there was no benefit to ultrasonographic evaluation.

Dr. Leveno's point about the therapeutic role of ultrasonography does relate to the fact that what we may be observing is that clinicians in 1986 to 1988 reacted more aggressively with therapy when an abnormality was detected by ultrasonography than clinicians who only had a report of a change of bimanual examination. We cannot prove that with these data.

Dr. Leveno suggests developing an ultrasonographic method for risk assessment. This would require a much larger sample size (Papiernik and Kaminski used 7000 patients for their pelvic examination risk assessment). Ultimately, the value of risk assessment lies in its ability to allow intervention to reduce preterm birth. In this article we described our ultrasonographic and bimanual pelvic examination criteria for identifying patients as being at increased risk, which allowed intervention, and then compared the ultimate result of the impact on preterm birth rates. We encourage further work on ultrasonographically based risk assessment, but have shown that there is no apparent benefit to ultrasonography versus bimanual examination for surveillance of the cervix.

I think the other comment about the possible effect of bladder filling on uterine activity may also be relevant. Certainly we see many patients at risk for preterm labor who report much more frequent contractions when they have a full bladder; in fact, when they void the uterine activity is then reduced. This is speculation at this point.

The vagaries related to diagnosis mentioned by Dr. Leveno are well accepted. I suggest that the value of this study does not rest on the diagnosis of preterm labor, however, that finding of preterm labor may be an indicator of potential problems. We hope to continue our work and study the ultrasonographic information we have collected to try prospective risk assessment as Bouyer and others have done with an actual relative risk based on cervical length. I think we should be able to do that, as Dr. Leveno suggested.

Dr. Bloom asked how we manage the patient with cervical effacement and dilatation without uterine contractions. In this study, the managment was determined by the attending physician. Our suggestions would be to review the patient's clinical circumstances and to monitor uterine activity. This may occur in the asymptomatic patient who should reduce activity and have increased surveillance, even if she were at low risk for preterm birth.

Dr. Ansbacher's comment about the indigent population is a good one. There has been extensive work in Philadelphia that suggests that treatment or interventions that are successful in one population for prevention of preterm birth may not work in another. We cannot address that at this point; it would be only speculation.

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Sacrospinous ligament fixation at the time of transvaginal hysterectomy

Stephen H. Cruikshank, MD, and Donald W. Cox, MD

Minneapolis, Minnesota, and Morgantown, West Virginia

Sacrospinous ligament fixation of the vagina was performed on 48 of 135 patients at the time of transvaginal hysterectomy. All 48 patients in the group had at least moderate or severe uterovaginal prolapse and symptomatic pelvic relaxation, which is described herein. In five patients cystoceles developed, in two patients rectoceles developed, and one patient has had vault prolapse subsequent to surgery. Morbidity was minimal. Postoperative results indicate that sacrospinous ligament fixation of the vagina can be a useful adjunctive procedure when performed at the time of vaginal hysterectomy. (Am J Obstet Gynecol 1990;162:1611-9.)

Key words: Sacrospinous ligament fixation, uterovaginal prolapse

Vaginal vault prolapse is considered an infrequent yet tragic (by the patient) complication after hysterectomy. Estimates in recent literature of its incidence range from 0.2%[1] to 1.0%.[2] The literature is replete with methods of repairing vault prolapse. Largely because of the work of Randall and Nichols,[3, 4] the use of sacrospinous ligament fixation to correct this condition has had a resurgence in the United States. Consistent with the consensus in the literature, Morley and DeLancey[5] have characterized this procedure as being for therapeutic purposes only.

This article recommends that sacrospinous fixation be performed at the time of transvaginal hysterectomy as an adjunctive measure to be used with patients at risk for vaginal vault prolapse. We recount the results of such surgery on 48 patients and offer this article as a complement to a previously published report.[6] We hope the readers will read the discussions and our closing statement to get the full flavor of this presentation.

Material and methods

Sacrospinous fixation of the vagina was performed on 48 of 135 patients undergoing vaginal hysterectomy for benign disease. Besides the indications for operation listed in Table I, all 48 patients had moderate to severe uterovaginal prolapse with or without symptomatic pelvic relaxation. Moderate uterovaginal prolapse was defined as the presentation of the cervix past the midportion of the vagina or to the introitus as a result of Valsalva's maneuver (Fig. 1). Severe uterovaginal prolapse was defined as presentation of the cervix past the introitus with or without Valsalva's maneuver (Fig. 2). The uterosacral-cardinal ligament complex was totally lax (surgically weak) or nonexistent in all 48 patients at the time of operation. These structures were unavailable to shorten or attach for support, although an attempt was made. Only the material relevant to the use of the sacrospinous fixation at the time hysterectomy is discussed. Other important details of this operation have been presented by Nichols and Randall,[4] Miyazaki,[7] and, most recently, Morley and DeLancey.[5]

The ages of the patients ranged from 33 to 81 years with a mean of 50 years. These patient characteristics were noted: age, weight, surgical indications, parity, and secondary diagnoses. All patients were screened with Papanicolaou smears and colposcopy when indicated. Patients gave informed consent for all procedures. The surgeons included one faculty member (S. H. C.), a gynecology resident, and at all times the referring physician, who was present to learn the procedure.

One hundred thirty-five patients underwent transvaginal hysterectomy as described in two standard texts.[4, 8] Forty-eight of these patients fulfilled criteria as defined above to have a sacrospinous fixation performed as well. A previously reported method[6] of attaching the uterosacral-cardinal ligament complex to the vaginal membrane for prevention of posthysterectomy vault prolapse was attempted in all cases (Fig. 3). In all 48 cases the laxity or lack of the uterosacral-cardinal ligament complex made it difficult to shorten or attach these for support. Therefore, after the hysterectomy was completed, the sacrospinous ligament

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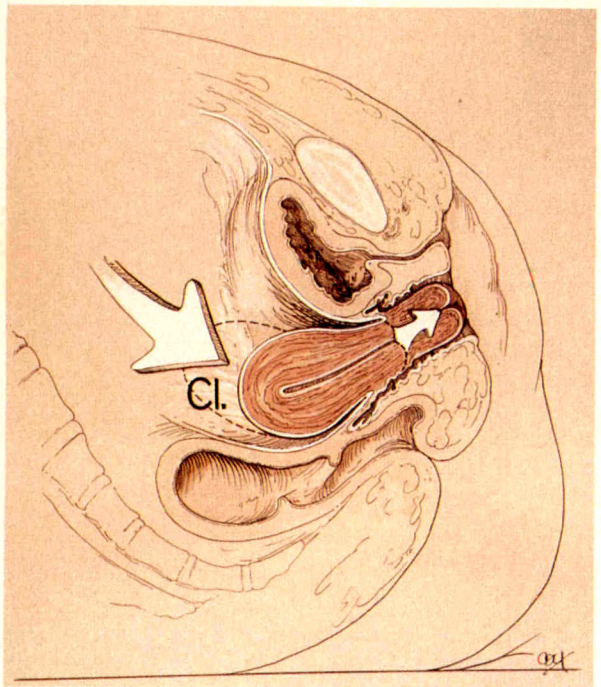


Fig. 1. Moderate uterovaginal prolapse.

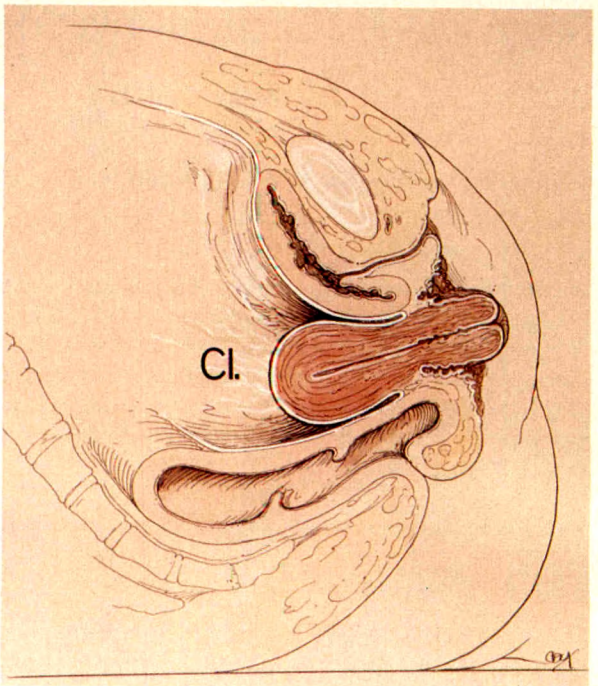


Fig. 2. Severe uterovaginal prolapse.

Table I. Indications for operation

Primary indication	*No. of patients*	*No. of patients with concurrent uterovaginal prolapse (only)*	*No. of patients with concurrent symptomatic relaxed vaginal outlet and uterovaginal prolapse*
Stress urinary incontinence	4	1	3
Grade 2 or 3*	9	6	3
Refractory dysmenorrhea	14	10	4
Recurrent postmenopausal bleeding	5	5	0
Dysfunctional uterine bleeding	16	10	6
TOTAL	48		

*Includes patients desiring sterilization with biopsy-proved grade 2 or 3 cervical intraepithelial neoplasia.

was identified. The ligament fixation procedure was performed as follows: (1) The posterior vaginal wall was opened to the apex and the rectovaginal space entered. (2) This was dissected with the operator's finger to the level of the ischial spines. (3) At that time the descending rectal septum (pillar) was perforated, opening the pararectal space (Fig. 4). With additional blunt dissection, the ischial spine and the coccygeus muscle–sacrospinous ligament were palpated and identified. (4) No. 2 Vicryl sutures were placed through the ligament (Fig. 5). These were held and left untied until any additional reconstructive procedures were completed. (5) Last, the sacrospinous ligament fixation was carried out with the use of both safety and pulley stitches[4] (Fig. 6).

Results

Transvaginal hysterectomy was accomplished in all 135 patients. Forty-eight adjunctive sacrospinous fixations of the vagina were carried out in these same patients. There were no injuries to the rectum, nerves, or bladder. In two cases, significant bleeding occurred from the perirectal veins, necessitating transfusion. The bleeding was stopped and there were no adverse sequelae as a result of injury to these vessels.

The morbidity and complications were low. All patients received prophylactic cephalosporin antibiotic therapy. Forty-four (92%) of the 48 patients remained afebrile throughout the postoperative course. Of the four patients with febrile morbidity (oral temperature of ≥37.9° C), three had a urinary tract infection and

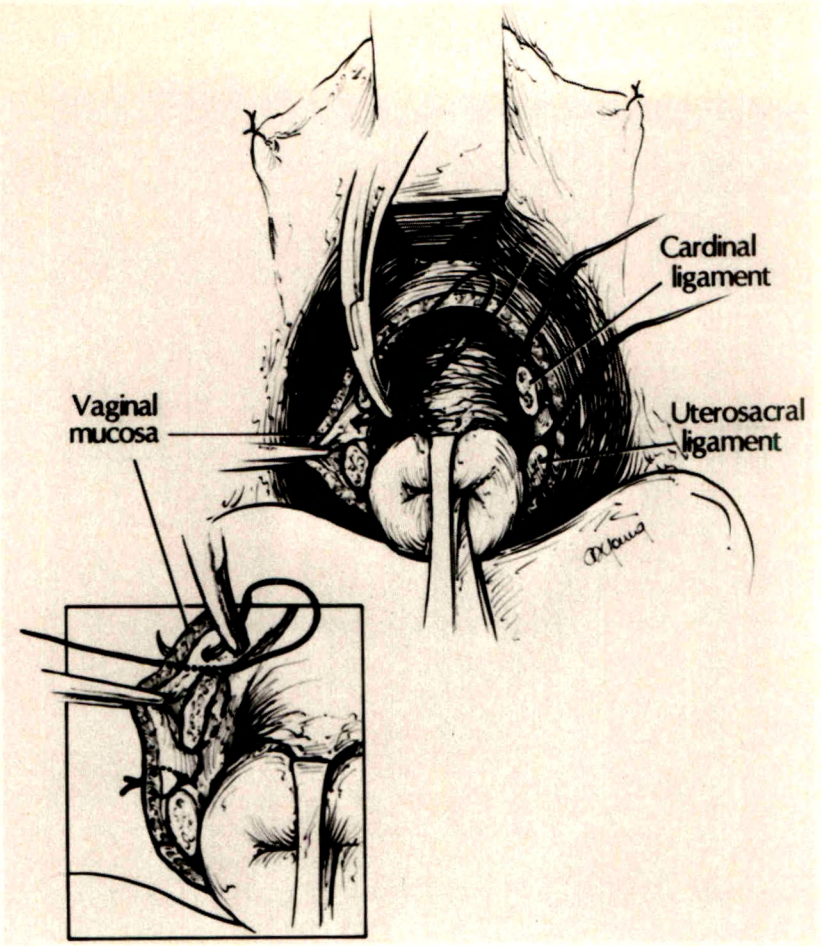


Fig. 3. Uterosacral and cardinal ligaments sutured to vaginal membrane. (From Cruikshank SH. AM J OBSTET GYNECOL 1987;156:1433-40.)

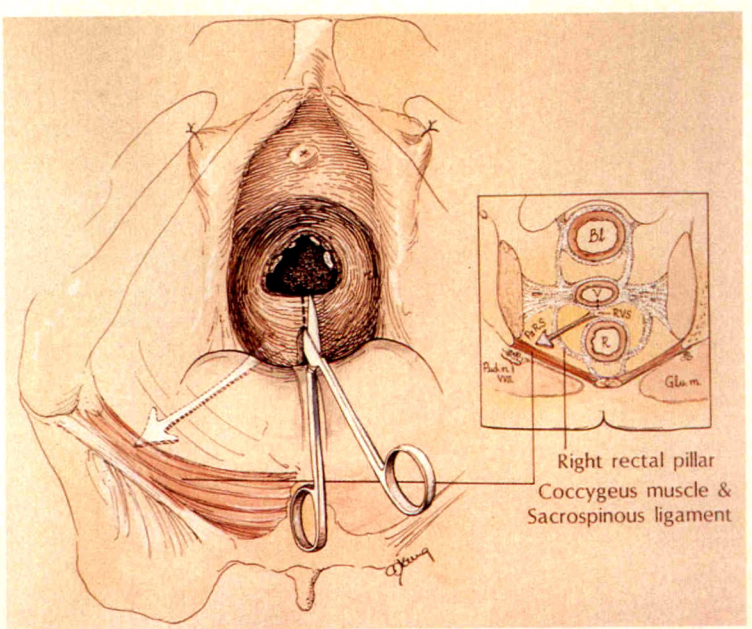


Fig. 4. Opening pararectal space *(arrow)* to identify coccygeus muscle.

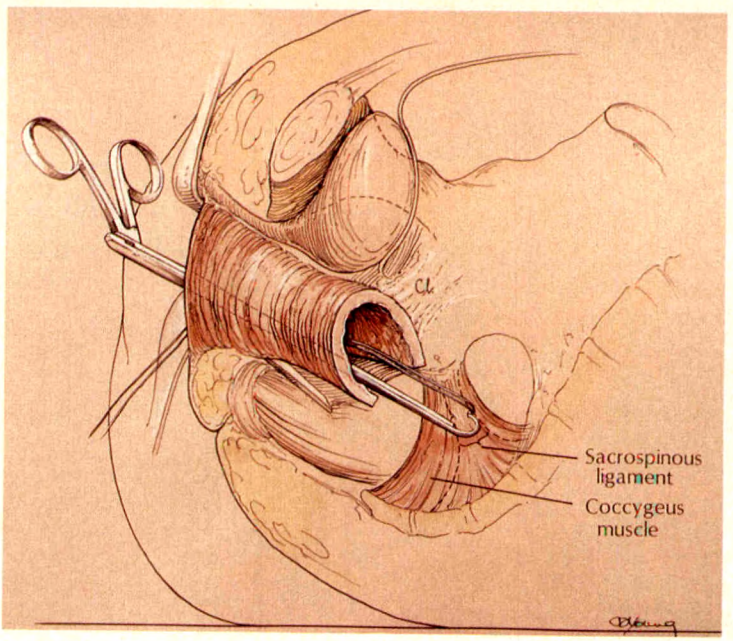


Fig. 5. Use of Miya hook to place sacrospinous ligament sutures.

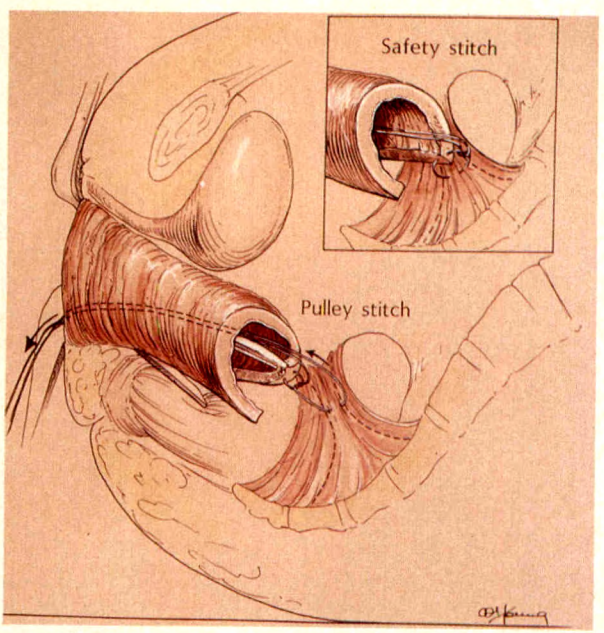


Fig. 6. Demonstration of safety and pulley stitches.

one had no demonstrable cause. The average blood loss was 290 ml for all procedures; average blood loss for sacrospinous ligament fixation was 100 ml. The average time for the entire operation was 2 hours 20 minutes (in a teaching setting), and the average time of the sacrospinous fixation procedure was 18.5 minutes. The average hospital stay was 6.2 days.

Four patients with concomitant anterior colporrhaphy were unable to urinate before discharge from the hospital. All were sent home with Foley catheters in place. All four patients have urinated since then. Two patients had transient stress incontinence from the sacrospinous procedure, but this complication resolved in both cases. Twenty patients complained of right buttock pain. All had spontaneous resolution by their 6-week postoperative checkup. All patients have been followed up from 8 months to 3.2 years without evidence of posthysterectomy vaginal prolapse, except in one patient. All patients were examined 6 weeks postoperatively. In both the supine and the standing position the patients were asked to elicit a Valsalva maneuver. The mean follow-up time has been 2 years.

Subsequent minor complications were without sequelae. In five patients anterior wall relaxation developed postoperatively without evidence of stress urinary incontinence. None of these had anterior colporrhaphy with our initial procedures. In two patients rectocele developed postoperatively. Neither had a posterior colporrhaphy with the initial operation; they elected not to have this complication repaired. Twenty-five patients had anterior colporrhaphy for urinary stress incontinence and/or symptomatic anterior vaginal wall relaxation. Eighteen patients had posterior colporrhaphy in addition to anterior repair. Five patients had an enterocele repaired, and seven additional patients had posterior colporrhaphy only. To date there has been one reported case of posthysterectomy vaginal vault prolapse.

Comment

Traditionally, sacrospinous fixation has been regarded as a therapeutic tool to be used only for repair

of vaginal vault prolapse.[3, 5] However, I feel that this procedure also may be used as a prophylaxis (as defined herein) against posthysterectomy vault prolapse. Not every vaginal hysterectomy patient is a candidate. If there is a loss of pelvic supportive structures (uterosacral-cardinal ligament complex) noted at the time of hysterectomy, an attempt to use their remnants should be made. However, sacrospinous fixation as an adjunct will prevent further vault prolapse. Nichols and Randall,[9] in their most recent textbook, state that without strong pelvic support a sacrospinous colpopexy is easy to perform after vaginal hysterectomy.

The 48 patients in this study represent only 35% of the vaginal hysterectomies performed during this time period. I stress again the point that the adjunctive sacrospinous fixation is not to be used universally in all vaginal hysterectomies. In these other 87 patients the uterosacral-cardinal ligament complex was attached only, and a sacrospinous ligament fixation was not required.

Previously a method was described that uses the pelvic supportive structures (the cardinal-uterosacral ligament complex) to help prevent subsequent prolapse.[6] These steps hold the vagina in its almost horizontal position above the levator ani; however, if these supportive structures are not present, the vaginal apex is still at risk for prolapse. In all 48 patients the apex was drawn past the introitus after the hysterectomy and any plastic repair. We feel it is appropriate during transvaginal hysterectomy to attempt support of the vagina in its normal anatomic position. Moreover, if moderate or severe uterovaginal prolapse exists as well, either as the main indication or as a secondary diagnosis, the pelvic surgeon should use the sacrospinous fixation to correct this, thus preventing future complications and sparing the patient from further procedures. Sacrospinous ligament fixation is not to be performed universally at the time of hysterectomy. Out of 135 patients undergoing vaginal hysterectomy, only 48 fulfilled the prerequisites for sacrospinous fixation of the vaginal vault. We feel this is an appropriate adjunctive-prophylactic procedure if strict criteria are met: (1) total laxity of the uterosacral-cardinal ligament complex, (2) moderate to severe laxity of the supportive structures and the ability to pull the vaginal apex to or past the introitus after hysterectomy and other plastic procedures, and (3) total procidentia at the time of hysterectomy.

Various principles of vaginal fixation during hysterectomy are recognized today. At all times the surgeon should note the laxity of the supporting structures and attempt to repair this at the initial operation.

Transvaginal hysterectomy offers a good opportunity to prevent future vaginal prolapse. Considering the results of this study, it seems feasible to add the sacrospinous fixation as a procedure in cases of vaginal hysterectomy presenting with moderate to severe uterovaginal descensus and loss of pelvic support. The procedure carries minimal morbidity, supports the vaginal apex, and provides the pelvic surgeon with an additional prophylactic measure against posthysterectomy vaginal prolapse.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. GEORGE W. MORLEY, Ann Arbor, Michigan. At the outset, I wish to compliment the authors on their well-presented thesis and on their endeavor to put forth an additional surgical procedure to prevent vaginal vault prolapse after vaginal hysterectomy. In the interest of time, however, whereas I strongly believe sacrospinous ligament fixation as a *treatment* of vaginal vault prolapse is a significant step forward in our *therapeutic* armamentarium, I must respectfully challenge their recommendation of it at the time of vaginal hysterectomy as a *prophylactic* measure against vaginal prolapse in the future. With the possible exception of a total procidentia, I must question the indication for this operation as an adjunct to vaginal hysterectomy.

In the manuscript it is stated that all 48 patients on whom the prophylactic procedure was performed, had moderate to severe uterovaginal prolapse with or without symptomatic pelvic relaxation. I personally think the more traditional definitions of uterine prolapse could have been used rather than the terms *moderate* and *severe* since most textbooks of gynecology describe uterine prolapse by degrees. In the authors' terms, however, how many cases were classified as moderate and how many as severe? Also were there any third-degree procidentias in their series?

It is also stated that the uterosacral and cardinal ligament complex was totally lax or nonexistent in all 48 patients. One wonders what method was used to ascertain this impression since in my experience attach-

ment of the sacrouterine and cardinal ligaments to the vaginal apex (even though these ligaments may be markedly attenuated), high closure of the peritoneum, *and* the McCall-type culdoplasty have worked most satisfactorily as a preventive procedure.

In this study the authors performed a sacrospinous ligament fixation prophylactically on 48 of 135 patients undergong *vaginal* hysterectomy, giving a frequency of performance of 35.5%. And yet in their own introduction they quote from a review of the literature an actual incidence of vaginal prolapse after *both* abdominal and vaginal hysterectomy (with almost an equal distribution) a range of only 0.2% to 1%. Given then a 0.5% incidence of vaginal prolapse after vaginal hysterectomy alone, 200 patients would have to undergo this prophylactic procedure to prevent one prolapse instead of one patient undergoing it therapeutically at a later date.

In a further effort to compare the *infrequency* of vaginal vault prolapse with the *frequency* of hysterectomy, the most common major gynecologic procedure we do, I reference one report from the literature. A number of years ago, Symmonds and Pratt[1] from the Mayo Clinic reported that over a 15-year period, when >15,000 hysterectomies were performed in their institution, only 24 of these patients were treated for vaginal prolapse there during the same time period. They stated in their article, "Even if we allow for the possibility that an equal number of patients with vaginal prolapse may have obtained treatment of prolapse elsewhere, the incidence of prolapse following hysterectomy performed at this clinic has not been great."[1]

Finally, the risk/benefit ratio must be considered since this procedure is not without complication; i.e., excess bleeding requiring blood transfusions, sciatic or pudendal nerve inpingement, and postoperative sepsis. There have been at least two deaths probably related to this procedure.

In closing, the role of the discussant is first to anticipate the questions of the profession and second to represent the welfare of the patients who are possible candidates for any procedure that might be recommended. With apologies to the authors but in feeling a responsibility as the discussant, I must state that I consider the sacrospinous ligament fixation as a *prophylactic* procedure unwarranted in most situations!

I challenge the prophylactic procedure as adjunctive treatment after vaginal hysterectomy for these reasons: (1) because of the infrequency of vaginal prolapse when compared with the frequency of hysterectomy, (2) because of the operative risks and postoperative complications, which when encountered may be significant, (3) because of the additional cost (should there be a charge) of the procedure to the patient or payor, and (4) because of the potential failure of the *prophylactic* procedure in the future. Sixty-six percent or two thirds of our patients treated therapeutically at Michigan[2] experienced their initial symptoms of prolapse longer than 5 years after hysterectomy. The short-term follow-up of the patients treated prophylactically in the authors' series had a mean of only 21 months.

I have for Dr. Cruikshank one additional question out of curiosity. What was the incidence of prophylactic bilateral oophorectomy in your overall series?

I thank you for the invitation to discuss this manuscript, and again my apologies to the essayist.

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DR. LESTER A. BALLARD, JR., Cleveland, Ohio. At the Central Association meeting in 1986, Dr. Cruikshank presented a paper entitled, "Preventing Posthysterectomy Vaginal Vault Prolapse and Enterocele During Vaginal Hysterectomy," in which he described 112 consecutive vaginal hysterectomies where there were identifiable uterosacral cardinal ligaments. He described his technique of shortening and attaching these ligaments to the vaginal vault for vault support, as well as a technique for enterocele prevention with the use of high peritoneal ligation incorporating the anterior wall of the rectum to close the posterior cul-de-sac. These 112 operations were done from July 1983 to March 1986, and the patients had a mean age of 30, ranging from 23 to 69 years. In my discussion of his paper, I asked what he did when the uterosacral cardinal ligaments were nonexistent or stringlike and not strong enough to support the vaginal vault, as in the older postmenopausal patient with severe prolapse. I mentioned that 38 (34.5%) of our 110 sacrospinous ligament fixations where there was third-degree uterine prolapse (mean patient age 63.5 years) were required as a primary adjunct to vaginal hysterectomy to maintain adequate vaginal depth and axis.

In their article the authors described a subsequent series of 135 vaginal hysterectomies where 48 patients required a sacrospinous fixation for vault suspension. This group of patients had a mean age of 50 (range 33 to 81 years) with the longest follow-up being 3.2 years. The authors have found sacrospinous ligament fixation to be a "useful adjunct" as a primary procedure done at the time of vaginal hysterectomy.

The indications for Dr. Cruikshank's vaginal hysterectomies in 1986 were dysfunctional uterine bleeding, grade 2 and grade 3 cervical epithelial neoplasia, refractory dysmenorrhea, stress urinary incontinence, recurrent postmenopausal bleeding, and symptomatic pelvic relaxation. In this report the indications were the same as in 1986, except there was no separate symptomatic pelvic relaxation group. The authors included 32 cases of vaginal prolapse and 16 cases of relaxed vaginal outlet with symptomatic uterovaginal prolapse

in these original five categories. I would have expected these patients to present with symptomatic pelvic pressure, bearing-down discomfort, protrusion, bleeding as a result of irritation, and urine irritability.

The authors illustrated and described patients with moderate degrees of prolapse, defined as the presentation of the cervix past the midline portion of the vagina or to the introitus, and severe prolapse, defined as presentation of the cervix past the introitus but showing the body of the uterus in the vagina.

It is interesting that Drs. Morley and DeLancey[2] refer to the criteria of Wilson and Carrington, which describe a first-degree prolapse as the cervix being between the level of ischial spine and vaginal introitus, second-degree prolapse as the cervix protruding through the introitus while the corpus remains in the vagina, and third-degree prolapse as complete prolapse of both the cervix and body of the uterus past the introitus and the entire vaginal canal everted. Therefore Dr. Cruikshank's moderate prolapse is Drs. Morley and DeLancey's first-degree, and Dr. Cruikshank's severe is Drs. Morley and DeLancey's second-degree and questionably third-degree together. Can the authors tell us how many cases were in the moderate and severe categories and did they include complete procidentia in the severe group?

The authors described uterosacral cardinal ligaments as totally lax or nonexistent in all 48 patients. Their structures were unavailable to shorten and attach for support although an attempt was made. They presented three criteria for adjunctive prophylactic use of the sacrospinous ligament fixation at vaginal hysterectomy: (1) total laxity of the uterosacral cardinal complex, (2) moderate to severe laxity of the supportive structures and the ability to pull the vaginal apex past the introitus after hysterectomy and other plastic procedures, and (3) total procidentia. Being able to pull the vaginal apex past the introitus after removal is a new criterion. I certainly concur with the third criterion of total procidentia. Does one have to have all three criteria or just one or two?

As a result of the authors' follow-up (mean 2 years), five anterior wall relaxations and two rectoceles were found; none of these patients had associated anterior and posterior colporrhaphy at the time of the sacrospinous ligament fixation. It is interesting that 37.5% of their patients had anterior-posterior repairs, 14.6% had anterior repairs only, 14.6% had posterior repairs only, and 33.3% had neither anterior nor posterior repair. Five patients had enterocele repairs, and one had vault recurrence.

In our current series of 268 sacrospinous ligament fixations, 233 (87%) of our patients had anterior-posterior repairs, 29 (10.7%) had posterior repairs only, 3 (1.1%) had anterior repairs only and 3 (1.1%) had no repair. Six had vault recurrences. Because of our original anterior wall recurrences and anterior enterocele with vault recurrence, I have increased the percentage of anterior-posterior wall repairs, even if only minor degrees of weakness are evident, to attempt to prevent these recurrences.

In Dr. Nichols' series of 163 patients, 59 (27.6%) cases were primary. In our own series of 268 sacrospinous fixations, 79 (29.5%) cases were primary. Dr. Nichols and I feel that primary sacrospinous fixation should be done at the time of vaginal hysterectomy when there are no surgically useful uterosacral cardinal ligaments for support of the vaginal vault. When cardinal uterosacral strength is lacking, an alternate method for vault suspension should be found. I would prefer not to rely on inadequate uterosacral cardinal ligaments for support or to have to depend on flimsy perirectal fascia and supralevator fascia support, for which one sacrifices depth and caliber. The latter procedure is good in the patient who does not want to maintain coital capacity.

I concur with Drs. Morley and DeLancey that prophylactic use of sacrospinous ligament fixation for "usual" or mild to moderate degrees of uterine prolapse is not usually needed and is an additional unnecessary financial burden. Hoerr's law, as used at the Cleveland Clinic, states, "It is difficult to make the asymptomatic patient feel better with surgery." In patients with good uterosacral cardinal ligaments that can be shortened for vault suspension, there is no need to perform a sacrospinous ligament fixation. However, in the patient with severe and complete uterine prolapse without surgically usable or identifiable ligaments, I would prefer to use sacrospinous ligament fixation. Drs. Morley and DeLancey also state that ". . . sacrospinous ligament fixation should be classified as a therapeutic procedure with the only reservation possibly being in patients with complete uterine prolapse as defined by Wilson and Carrington."

I will look forward to follow-up reports of Dr. Cruikshank's 1986 and present series regarding the prevention of vaginal vault prolapse.

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Dr. Scott Snyder, Columbia, Missouri. I would like to know how many of the 138 patients had retropubic urethropexies and how this influenced the decision to do the sacrospinous ligament fixation.

Dr S. Robert Kovac, St. Louis, Missouri. I have a question to ask both Dr. Cruikshank and Dr. Morley. I'm a little bit confused, and maybe they can help me understand this better. Are we really quite sure what

the uterosacral-cardinal complex does anatomically to prevent vault prolapse? We need to decide whether this ligament complex supports the vagina or simply directs the vagina over the levator plate for support. Vault prolapse may be the result of a problem at a much higher pelvic level; therefore I think it is probably folly to rely on that particular complex as the sole definitive support of the vagina.

We must decide what anatomically we are attempting to accomplish with any type of plication procedures involving these ligaments. If we believe that these ligaments can prevent vault prolapse, then I think we must accept the consequences that we are going to have vault prolapse after some hysterectomies whether they are performed abdominally or vaginally.

However, sacrospinous fixation does not anatomically correct the cause of vault prolapse, but it does indirectly direct the vagina over the levator plate, perhaps better than plication procedures.

It appears to me that "the horse is out of the barn, and we forgot to close the gate"; now we're trying to catch up with the problem of preventing future vault prolapse. I think the most important issue is to actually determine and agree on what anatomic structures cause vault and uterine prolapse. Then we as gynecologic surgeons can design a specific surgical procedure to correct this problem and not rely on whatever we have used in the past to prevent this condition now and in the future.

Dr. Alan G. Waxman, Gallup, New Mexico. I wonder if, as Dr. Cruikshank expands his series, it might not be useful to introduce a comparison group, perhaps of the same patient population, randomized and operated on by the same surgeons so we can see if there really is efficacy from this procedure in the long run.

Dr. Bruce C. Richards, Lakewood, Colorado. In the appropriate case—and not to get into the controversy—for those that are interested in doing this procedure, I would endorse the notion of using the Mia hook. It is very facilitative.

Dr L. Russell Malinak, Houston, Texas. Was the cuff left open or was it closed in your patients with sacrospinous fixation? Does it matter?

Dr. Cruikshank (Closing). I am humbled. First of all, I would like to thank the discussants. I'm reading the book *Final Flight.* A quotation from it goes like this: "Confront the enemy with the tip of your sword against his face," and that's what I'm going to do in this debate.

The first thing I would like to say in respect to taking care of pelvic floor relaxation is that each aspect must be addressed to obtain optimal results. I think we need to keep that in mind when we're evaluating the patient in the office. I think the history and physical examination are probably the most important things, with the patient in the erect and the supine positions, not under anesthesia.

Once you make your surgical decision and find out in which quadrant or which anterior-posterior area you have a defect, then you can plan your repair; then a good pelvic examination with the patient under anesthesia should be done as well.

I anticipated this discussion so I brought one certain article to help me. This is Dr. Morley's article on sacrospinous fixation. He questions my indications and asked how many patients had procidentia. Procidentia was found in 8 patients. Severe prolapse as I defined it occurred in 24, moderate prolapse was found in 16.

To back my manuscript further, the abstract of Dr. Morley and Dr. DeLancey says that while 57 patients had a posthysterectomy complete vaginal prolapse, 38 patients had an incomplete vaginal prolapse. Again on page 873 it is stated: "The indication for operation was total vaginal prolapse in 57 patients (vaginal apex below the introitus), incomplete vaginal prolapse in 38 (vaginal apex at or above the introitus), and enterocele in five."

Now, if you recall my illustrations, the only differences between my criteria and his criteria is that the uterus is in situ in our patients. Once it's out, I then reexamine the patient and I've obtained his criteria. If I've done plastic repairs and I can still get the apex past the introitus or down to the introitus, then I've got the same problem as he does; that's why we have to take each defect and look at it individually and not just do a hysterectomy and say we solved it.

Uterine prolapse is not the cause of genital prolapse. It's a result. So if we have anterior wall relaxation, posterior wall relaxation, or enterocele, that's the result of genital prolapse; do we really know what causes it? Well, we're trying to find out, but we all have techniques that we're trying to use to cure it, and that's what I'm doing.

I would also like to read from Dr. Morley's article something else that parallels my manuscript (remember that the only difference is that the uterus is in situ in my patients until the hysterectomy is done): "Simply stated, all relaxations should not be treated as cystocele-rectocele." I have the feeling that that's what he wanted me to do as long as the uterus was in situ. This in my opinion would result in posthysterectomy degrees of prolapse.

Now, on page 878 of the article, I read: "An incomplete prolapse is present when any pathologic descensus down to the introitus exists. Any degree of descensus beyond this point is classified as a total vaginal prolapse. If further description of the prolapse is required, mensuration from the introitus as a reference point could be used."

I think I attempted to define that, and I tried to do that in the office when the patients came in; if they could perform a Valsalva maneuver of the uterus down to the introitus or past the introitus, there was more abnormality than just uterine prolapse. So I didn't want to do a hysterectomy and just say, "See you back after a while."

The complications in Dr. Morley's patient population were no different from the complications in mine or the complications of Dr. Nichols, and they're not as bad as the complications we see from episiotomies and ce-

sarean sections. We've got to do something about these routine—what we call therapeutic—operations that wreak a lot of havoc and have more morbidity than a sacrospinous fixation.

Now, 0.2% to 1% as the incidence of vault prolapse is in the recent literature. Gynecology is very interesting. What is old literature? In the 1960s reports say vault prolapse occurs in 1% to 43%; is that the old literature? And in obstetrics "current" means "5 years old." In gynecology though, what's old? So the 0.2% to 1% figure represents the literature of the late 1970s and 1980s. But in the older literature, in the 1960s, it was as high as 43%.

I spent some time in the Third World just this summer, and I can guarantee that some things are different. I was in Portugal. We had a whole ward of women who were seen with uterovaginal and vaginal prolapses, and there was close to if not more than 43% incidence. It may be their life-style or that the hysterectomy was performed wrong the first time. I don't know. It was very impressive.

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Reproductive performance after methotrexate treatment of ectopic pregnancy

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The purpose of this study was to examine return of reproductive potential, hysterosalpingographic findings, and time to conception in patients treated with methotrexate and citrovorum factor for unruptured ectopic pregnancy. Fifty-seven patients with unruptured ectopic pregnancies <3.0 cm in greatest dimension were treated with methotrexate and citrovorum factor. The mean time from resolution of the ectopic pregnancy to return of menses was 26.0 (0 to 157) days. Forty-four patients were available for follow-up (2 to 15 months). Nineteen of 23 patients who had hysterosalpingograms demonstrated patency in the ipsilateral tube. Fourteen patients desired pregnancy; 11 of 14 (78.6%) were successful, with 10 of 11 (90.9%) having an intrauterine pregnancy, whereas one of 14 (9.1%) were extrauterine gestations. The mean time from first attempt to achieving pregnancy was 2.3 (1 to 4) months. We conclude that methotrexate and citrovorum factor treatment of unruptured ectopic pregnancy is associated with subsequent tubal patency and does not impair return of menses. Most importantly, the pregnancy rates after this form of therapy appear to be better than those achieved by traditional surgical methods, and are comparable to results after laparoscopic salpingostomy. (AM J OBSTET GYNECOL 1990;162:1620-4.)

Key words: Ectopic pregnancy, methotrexate, reproductive function

Previously only one third of women with a previous ectopic pregnancy had a subsequent live birth.[1, 2] More than 50% of these women were subsequently unable to conceive.[3] Although operative strategy has changed toward more conservative management, only 68% of patients treated conservatively with microsurgical techniques conceive and only 56% will have an intrauterine pregnancy.[4] Thus there is a need to seek treatment modalities with better reproductive potential.

Recent reports increasingly advocate the use of methotrexate and citrovorum factor for treatment of unruptured ectopic pregnancy.[5-7] Because it is safe, effective, and can be performed on an outpatient basis, medical treatment offers an attractive alternative to the patient and clinician. Tubal rupture and significant methotrexate–citrovorum factor drug-related side effects do occur, but these occur in less than 5% of patients, making this a very safe treatment.[7] The 5% incidence of rupture is comparable with the 3.5% to 10% incidence of persistent tubal ectopic gestation after conservative surgical procedures. In such patients a second surgical procedure or methotrexate chemotherapy is then required.[8, 9] Unanswered questions with regard to this form of therapy concern problems such as delayed restoration of menses, distorted tubal anatomy as a result of medical rather than surgical treatment, and poor reproductive performance.

To our knowledge no studies have addressed the question of subsequent reproductive performance in patients with ectopic pregnancy treated with methotrexate–citrovorum factor. In a large ongoing series, this article examines return of reproductive function in a group of women successfully treated with methotrexate–citrovorum factor for ectopic pregnancy and evaluates time to first menses, tubal patency, time to conception, and pregnancy location and outcome.

Material and methods

Beginning Nov. 1, 1987, an intensive screening program for the early diagnosis of ectopic pregnancy was begun at the University of Tennessee, Memphis. All patients without active liver disease diagnosed with unruptured ectopic pregnancies ≤3.0 cm in greatest diameter were eligible for outpatient treatment with methotrexate–citrovorum factor and were treated as previously described according to an Institutional Review Board–approved protocol.[7]

Until completion of treatment, defined as human chorionic gonadotropin (hCG) titer <10 mIU/ml, patients were asked to refrain from sexual intercourse. Patients were also counseled to use oral contraceptives, or double-barrier contraception for the 2 months after completion of therapy. Hysterosalpingograms were

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scheduled 7 to 12 days after the patient's first menstrual period. Patients were then counseled concerning pregnancy, and those desiring pregnancy were no longer required to use contraception.

Follow-up was performed every 2 to 3 months. Only those patients who completed therapy and underwent follow-up until March 1, 1989, are included.

Statistical analysis was performed with the life-table method. All values are reported as means ± 1 SD.

Results

During the study period 204 patients with ectopic pregnancy were diagnosed; 131 gestations (64.2%) were unruptured and 73 (35.8%) were ruptured. Of the 131 unruptured ectopics, 57 (43.5%) tubal pregnancies (study group) and one (0.76%) cervical ectopic pregnancy were treated with methotrexate–citrovorum factor.[10] Nine (6.9%) patients had ectopic gestations that regressed, whereas the remaining 64 (48.9%) were treated surgically. Of the 64 patients with unruptured ectopics treated surgically, 60 were not eligible for methotrexate–citrovorum factor treatment because of ectopic size or cardiac activity. The remaining four (6.3%) patients declined medical therapy.

Mean patient age was 26.9 ± 5.4 years (range, 16 to 38 years); gravidity ranged from 1 to 6 and parity ranged from 0 to 5. Twelve of the 57 (21.1%) patients in the study group had a previous ectopic pregnancy with six (50.0%) occurring on the right and six (50.0%) on the left. No patient had more than one previous ectopic gestation. Ten of 12 patients (83.3%) had previous salpingectomies for ruptured ectopics, whereas two had been treated previously with salpingostomies.

One to four doses of methotrexate–citrovorum factor were administered (mean, 2.5 ± 1.1 doses). The time from treatment to resolution (hCG titer <10 mIU/ml) ranged from 9 to 100 days (mean, 27.2 ± 16.5 days).

Forty-four of 57 (77.2%) patients with unruptured tubal ectopic pregnancies were available for follow-up; 13 (22.8%) were lost to follow-up. The time of follow-up ranged from 2 to 15 months.

Mean time to first menses, calculated from the last day of treatment, was 21.7 ± 26.0 days (0 to 157 days). Only one patient had delay of menses beyond 45 days, and 42 of 44 patients described regular menstrual periods with intervals ranging from 28 to 35 days.

Twenty-three patients had hysterosalpingograms after methotrexate–citrovorum factor treatment. Of 43 tubes present, 35 of 43 (81.4%) were patent with a normal appearance, and 8 of 43 (18.6%) were occluded. Two of the eight occluded tubes (25%) had cornual obstruction; the remaining six (75%) were obstructed more distally with hydrosalpinx and distorted tubal anatomy. In 20 of 23 (87.0%) patients, at least one tube was patent, whereas 19 of 23 (82.6%) patients had tubal patency on the side involved with the ectopic implantation (Table I).

Of the 44 patients available for follow-up, 30 (68.2%) were either using birth control or were not sexually active. The other patients had actively attempted to become pregnant after treatment. Of these 14, 11 (78.6%) achieved pregnancy. Although one patient (9.11%) of the 11 had a repeat ectopic pregnancy in the contralateral tube treated with methotrexate–citrovorum factor, 10 of 11 (90.9%) achieved an intrauterine pregnancy. One of these intrauterine pregnancies ended with a spontaneous abortion, and the other nine have reached the second trimester or have been delivered. One of the 11 had only one tube, whereas the other 10 patients had both tubes present. Eight of the 11 (72.7%) had hysterosalpingograms before becoming pregnant, all of which revealed bilateral tubal patency. The mean time from treatment completion to diagnosis of pregnancy was 5.0 ± 2.6 (1 to 10) months. The mean time to pregnancy calculated from the first attempt at conception was 2.3 ± 1.0 (1 to 4) months.

Life-table analysis demonstrates the probability of pregnancy after completion of methotrexate–citrovorum factor treatment of unruptured ectopic pregnancy to be 25% at the end of 1 month and 87% after 4 months of attempted pregnancy (Fig. 1).

Comment

This study describes, for the first time, return of reproductive function after medical treatment (with methotrexate–citrovorum factor) of unruptured ectopic pregnancy, expressed as resumption of menses, tubal patency, time to conception, and pregnancy outcome.

Our overall tubal patency rate was 81.4%. This is comparable to that reported by Sauer et al.[6] in a similar series of unruptured ectopic pregnancies treated medically. In a surgical series, Mitchell et al.[11] described hysterosalpingograms obtained in 13 women whose ectopic pregnancies were removed by linear salpingostomy. Only four of 13 patients had bilateral tubal patency, whereas six of 13 had unilateral patency (four contralateral tubes, two ipsilateral tubes), and three of 13 had bilateral occlusion. Although our patient population is similar to that described by Mitchell,[11] the patients in our series were diagnosed at an earlier gestation as a result of our intensive screening methods.[12] Because of the earlier diagnosis and successful medical therapy, less tubal damage could be expected. In a comparable series, Vermesh et al.[13] demonstrated patency of the involved tube in 16 of 20 (80.0%) and 17 of 19 (89.0%) patients undergoing salpingostomy by laparoscopic and laparotomy approach, respectively.

Presumptive ovulatory function returned promptly

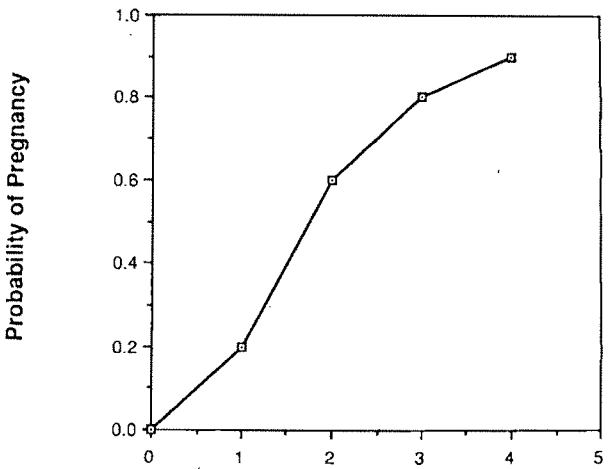


Fig. 1. Probability of pregnancy by time attempting conception after treatment with methotrexate.

Table I. Comparison of ectopic site with hysterosalpingographic findings

	Hysterosalpingogram findings			
	Patent		*Nonpatent*	
Ectopic site	*No.*	*%*	*No.*	*%*
Right (n = 18)	14	77.8	4	22.2
Left (n = 5)	5	100	0	00.0
TOTAL (N = 23)	19	82.6	4	17.4

after disappearance of hCG. In the majority of patients, normal menses returned just before completion of therapy or within the first 30 days after disappearance of hCG. In only one patient was this period longer than 45 days. Menses did not resume in this patient for 157 days at which time the patient sought treatment. The patient was morbidly obese and had withdrawal bleeding after a 10-day course of medroxyprogesterone acetate therapy. Kamrava et al.[14] showed that serum clearance of hCG may take up to at least 24 days after a conservative surgical procedure. Our mean time to disappearance of hCG is similar, although somewhat prolonged in a few patients with higher hCG titers. Thus use of methotrexate does not appear to unduly delay hCG disappearance or return of menses.

The probability of conception after methotrexate–citrovorum factor treatment is 25% and 87% at 1 and 4 months, respectively (Fig. 1). This is comparable to normal women with azospermic husbands who undergo artificial insemination with fresh semen. In one such series, Corson[15] found that 72% of pregnancies occurred by the end of the third cycle, a figure comparable to our study group (Fig. 1). However, our figures are somewhat superior to the surgical series of Vermesh et al.,[13] in which the pregnancy rate was 56% (10/18) in patients undergoing laparoscopic salpingostomy and 58% (11/19) in those treated by laparotomy salpingostomy. All pregnancies reported in this series were conceived within 6 months of operation. Our study is reassuring because 78.6% of patients (11/14) seeking pregnancy were able to conceive. However, our ability to draw firm conclusions is hindered by 22.8% of patients lost to follow-up after therapy completion and the small number of patients seeking pregnancy. It is also possible that the 44 patients available for follow-up and 14 patients attempting pregnancy are not representative of the entire study population.

On the basis of follow-up data available on patients treated with methotrexate for gestational trophoblastic disease, there does not appear to be an increased incidence of congenital malformation in subsequent pregnancies.[16] Although our study is not large enough to eliminate this possibility in this group of patients, it would seem unlikely given the current knowledge based on experience with gestational trophoblastic disease.

The intrauterine pregnancy rate of 90.1% in this series is superior to the 49% to 70% intrauterine pregnancy rate in patients treated by linear salpingostomy reported in a recent review.[16] In addition, our recurrent ectopic rate of 9.1% is comparable to the rate of 13% (0 to 22) reported in the same series. We speculate that the higher intrauterine pregnancy rate is not a result of methotrexate–citrovorum factor treatment alone, but a result of earlier diagnosis with an intensive screening program. By minimizing the time in which trophoblastic tissue can invade tubal mucosa, the risk of anatomic distortion with subsequent recurrent ectopic pregnancy is also lessened. We also hypothesize that medical therapy results in less tissue damage to the tube than any surgical procedure, regardless of how conservative the operation.

We conclude that methotrexate–citrovorum factor treatment of unruptured ectopic pregnancy does not impair return of menses, helps restore tubal anatomy as demonstrated by the hysterosalpingography, and does not appear to impair subsequent reproductive performance. The pregnancy rates after this form of therapy appear to be better than those achieved by traditional conservative surgical methods, comparable to laparoscopic salpingostomy, and comparable to normal women with azoospermic husbands who undergo artificial insemination with fresh semen. The principal value of this safe, effective form of treatment is that it bypasses the risk, cost, and morbidity of surgical intervention. This preliminary study is reassuring evidence that the benefits of methotrexate–citrovorum factor treatment are not offset by any loss of reproductive efficacy.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. BRYAN D. COWAN, Jackson, Mississippi. To my knowledge, the first report of successful treatment of an ectopic pregnancy with methotrexate occurred in 1982.[1] After this report, a few case reports depicted anecdotal experience of unusual presentations of ectopic pregnancies including cervical pregnancy,[2] cornual pregnancy,[3] and persistent trophoblast[4] after conservative surgical management of unruptured tubal pregnancies. In 1985 the first clinical study of methotrexate as primary treatment for ectopic pregnancy was reported at the fifty-third annual meeting of this association in New Orleans.[5] Dr. Steve Ory and his colleagues described six patients with confirmed unruptured tubal pregnancies that were treated primarily with methotrexate. Since then several institutions have reported their experience in treating tubal pregnancies with methotrexate.

This report addresses an important question that all of us who have treated or have considered treating patients with tubal gestations with methotrexate have asked: "Do patients who undergo this treatment have preservation of tubal and reproductive function?" I am impressed with the authors' results.

Some aspects of this study, however, make the ultimate interpretation of this data difficult. For example, we do not know the status of the unaffected tube in the 14 patients who were attempting pregnancy. It is entirely possible that the unaffected tube was perfectly normal and therefore posed no risk for repeat ectopic pregnancy on the contralateral side or impairment of fertility. If the 10 patients who conceived an intrauterine gestation were disproportionately composed of women with normal contralateral anatomy, a distinct reproductive advantage would be granted to this group. On the other hand, women with contralateral tubal disease would be at risk for repeat ectopic pregnancy, and reduced fertility. An additional shortcoming is the failure to specify an ampullary or isthmic location for the ectopic pregnancy. The data cannot be analzyed to determine if patients with ampullary or isthmic tubal pregnancies have the same clinical outcome and subsequent reproductive potential after treatment with methotrexate. The trophoblast may invade the muscularis more aggressively in isthmic ectopic pregnancies,[6] and the subsequent outcome of these patients may be different than ampullary gestations.

I agree with the authors that this form of therapy, on the basis of their data, does not appear to impair subsequent reproductive performance. However, before we embrace this information completely, subsequent studies by other authors and other institutions should confirm these observations.

The claim that this therapy reduces the risk, cost, and morbidity of surgical intervention for ectopic pregnancy cannot be supported. All patients in this study underwent laparoscopy to confirm the diagnosis. It is exceptionally difficult for most gynecologists to recognize an ectopic pregnancy at the time of laparoscopy and allow this pathologic condition to be untreated by operation. Most gynecologists would remove the ectopic pregnancy and forego the cost of medical treatment. However, I can foresee when it may become practical to treat ectopic pregnancies without operation. Visualization by either ultrasonography or laparoscopy is currently required to confirm the diagnosis of an ectopic gestation. When an ectopic gestation can be defined without the need for operation, methotrexate therapy may be the treatment of choice. Ultrasonographically guided direct injection of methotrexate into

the gestational sac has successfully cured women in whom the ectopic gestation could be visualized.[7] Once diagnostic operation can be avoided, the true potential for this therapy as the primary treatment for tubal pregnancies will be realized. We are greatly encouraged by the favorable reproductive outcome reported here.

I have two questions for the authors. First, have they considered intraoperative injection of any ectopic gestations with methotrexate? Second, are they aware of the condition of the contralateral tube in the 10 of 14 women with an intrauterine gestation, and three who have failed to conceive, and one with a repeat ectopic pregnancy?

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DR. M. WAYNE HEINE, Tucson, Arizona. The authors have provided additional information on return of reproductive function in patients treated medically for ectopic pregnancy. They studied return of menses, pregnancy rate, and pregnancy outcome. Menses returned within 26 days, and 82% of the affected tubes were patent after therapy. The pregnancy rate was 87% within 4 months, similar to donor insemination programs. The intrauterine pregnancy rate was 90%. This was compared with surgical treatment with a pregnancy rate of 57%, and the intrauterine pregnancy rate varies between 40% and 70%. The recurrent ectopic rate is similar in the two groups. Because of the restrictive criteria for a patient to enter the study, (i.e., tubal pregnancy of less than 3 cm in diameter), only 44 patients were available for follow-up of 2 to 15 months. Only 14 patients desired pregnancy. Because of this small number of patients (one patient in either direction), tubal pregnancy or abortion would alter the percentages greatly. The results are not comparable to the surgical method of treatment because the study patients had very early tubal pregnancies (less than 3 cm). The surgical series reported included more advanced tubal pregnancies. With more advanced tubal pregnancies there is more bleeding, distortion of the tubes, and invasion by the trophoblast. The method described by the authors is less costly and would save approximately $1200 per patient in our institution. There also should be less dissemination of trophoblastic materials with medical therapy.

The study would have been more informative if there had been an increased number of patients, and had alternated between medical and surgical therapy using the restrictive criteria. The comparison of reproductive function, morbidity, and cost would have been more meaningful.

DR. JOHN L. AUSTIN, Memphis, Tennessee. Dr. Stovall, what would be the appropriateness of a direct injection of methotrexate, perhaps during vaginal probe ultrasonography, in terms of both cost effectiveness and technical ability? Are you going to study this in the future?

DR. DANIEL A. RIGHTMIRE, Springfield, Illinois. Are the results so impressive that they preclude a prospective randomized trial?

DR. STOVALL (Closing). To update you on our progress, we have treated >80 unruptured ectopic pregnancies with methotrexate. Of these, 95% were successfully treated without further intervention. Of the three failures, two can be related to the presence of cardiac activity in advanced gestations with high hCG levels; the third rupture remains unexplained.

Current contraindications to methotrexate therapy include a size of ≥3 cm, rupture of the ectopic pregnancy, or the presence of cardiac activity. A study was recently reported in abstract form from Argentina in which the investigators treated ruptured ectopic pregnancies with methotrexate.

In the future, these contraindications outlined may become relative contraindications. Our group has treated approximately four patients with cardiac activity with low hCG levels, all of which have had successful outcomes.

To date, 16 pregnancies have occurred after methotrexate treatment; two of these were ectopics; and of some note, both were in the contralateral tube. Fourteen were intrauterine pregnancies. Thirteen of the fourteen intrauterine pregnancies are viable, and one ended with a spontaneous abortion.

The role of oral methotrexate in the treatment of this condition, the role of direct injection at the time of laparoscopy or at the time of vaginal ultrasonography (operative ultrasonography) remains uncertain. There are reports of oral methotrexate use, and there are reports with direct injection of methotrexate, potassium chloride, and prostaglandin. We have attempted direct injection with transvaginal ultrasonographic guidance on two patients. Both treatments failed.

CORRESPONDENCE

Editors' note: Readers may note we are publishing more Letters to the Editors in an effort to reduce the backlog and improve the publication time.

Treatment of twins with hydramnios

To the Editors:

The report by Lange et al. on the treatment of twins with hydramnios (Lange IR, Harman CR, Ash KM, Manning FA, Menticoglou S. Twin with hydramnios: Treating premature labor at its source. AM J OBSTET GYNECOL 1989;160:552-7) prompts several important questions that are not clearly answered in the title, text, or diagrams. What is the zygosity of each twin pair? Were the placentas monochorionic or dichorionic? What were the hematocrit values at birth? What was the prenatal diagnosis for each of these pregnancies? Last, did each twin have hydramnios or did only one fetus have polyhydramnios whereas the other had oligohydramnios, as reported by Chescheir and Seeds?[1]

If the treatment group included pregnancies complicated by both polyhydramnios and oligohydramnios, then Lange et al. have presented a remarkable improvement in outcome without resorting to infanticide or serial amniocentesis. It is hoped that the authors have reported a medical solution to the vexing problem of twin pregnancies with concurrent polyhydramnios and oligohydramnios.

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Hydramnios in twin pregnancy

To the Editors:

Lange et al. reported the results of treating six twin pregnancies that were complicated by hydramnios and premature labor (Lange IR, Harman CR, Ash KM, Manning FA, Menticoglou S. Twin with hydramnios: Treating premature labor at its source. AM J OBSTET GYNECOL 1989;160:552-7). Indomethacin was used both as a tocolytic agent and to reduce fetal urine output. The results are compared neither with previous cases, nor with controls in which this therapy was withheld, nor with cases in which other therapies were used.

We agree that hydramnios is a major cause of premature labor in twin pregnancy because it increases intrauterine volume above that caused by the twin pregnancy itself. Hydramnios may be caused by fetal anomalies, such as upper gastrointestinal tract obstruction or hydrops fetalis. Both of these anomalies may occur with increased frequency in twins. However, the most common cause of hydramnios in twin pregnancy is twin-to-twin transfusion, in which there are interfetal arteriovenous anastomoses in the parenchyma of monochorionic diamniotic placentas of monozygotic twins.[1] Hydramnios of the sac of the recipient may be accompanied by oligohydramnios of the sac of the donor, with the appearance of "stuck twin" in the donor. Twin-to-twin transfusion often results in premature labor in the early second trimester. Some cases are first seen clinically as acute severe polyhydramnios, which results in high perinatal mortality. Hydramnios in the sac of the recipient has been documented as being caused by fetal polyuria.[2] There usually is quite marked growth discordance.

In attempts prenatally to elucidate the causes of hydramnios in twin pregnancies, zygosity determination and placental anatomic studies are necessary. Several publications have documented the ability to distinguish monochorionic from dichorionic placentation in twins.[3] With the use of deoxyribonucleic acid restriction fragment length polymorphisms, zygosity can be diagnosed prenatally.[4] Postnatal documentation of placentation and zygosity is also mandatory.

It seems possible that pairs 1 and 6 of Lange et al. may have had twin transfusion syndrome to account for the hydramnios and growth discrepancy. It is not clear whether twins 5a and 6b both had congenital heart disease or whether there is a textual error.

We think that Lange et al. should clarify the issue of zygosity and placentation in their preliminary series and in any further publications. It is clear to us that hydramnios induced by twin transfusion has a distinctive pathophysiology, with recipient fetal polyuria. Twin pregnancies that are not monochorionic may have hydramnios of other causes. Alternative maneuvres, including repeat amniocentesis and selective birth, may be attempted in monochorionic twin hydramnios, but would not otherwise be appropriate.

We appeal to authors (and journal editors) to ensure that full information on zygosity and placental anatomy

is included in published data on complications and therapy in twin pregnancies.

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A complete list of references is available from the authors on request.

Reply

To the Editors:

We appreciate the comments on our article and we are happy to address issues that these authors have raised.

First, with regard to the zygosity of each twin pair, monozygotic dichorionic placentas were confirmed in two twin sets (twins 1 and 4) and dichorionic, diamniotic placentas were confirmed in the remaining twins. In two twins (1 and 5) no membrane was seen at initial assessment, which did raise the possibility of monoamniotic monozygosity twins. With treatment a membrane subsequently became visible.

In case 1, the working diagnosis was a twin-to-twin transfusion. In case 5 congenital heart disease in one twin was suspected. In the remaining twins, inasmuch as growth profiles and Doppler ultrasonographic studies were normal, the cause for the gross hydramnios was unexplained.

The hematocrit values varied between cases, from 41.3% to 63.1%, but between twins the mean difference was small, averaging 3.8%. In only one pair did the difference in hematocrit exceed 5% (A = 41.3%, B = 52.7%). There was no significant discordance in cord pH, blood gas values, or Apgar scores. There was hydramnios in both twins in all cases before treatment. In three cases one twin showed a more marked diminution in fluid with indomethacin treatment than that of the other twin.

Subsequent to this report five further cases have been treated in a similar matter. In one case, there was unequivocal oligohydramnios in one sac and hydramnios in the other. Treatment was maintained from 27 to 31 weeks' gestation and labor occurred within 24 hours of discontinuing indomethacin. Transient oliguria was noted in the twin with oligohydramnios. There was clinical evidence of a twin-to-twin transfusion.

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Study of preterm birth draws different interpretation

To the Editors:

Because we have participated in a multicenter trial of preterm birth prevention similar to that reported by Mueller-Heubach et al. (Mueller-Heubach E, Reddick D, Barnett B, Bente R. Preterm birth prevention: Evaluation of a prospective controlled randomized trial. AM J OBSTET GYNECOL 1989;160:1172-8) but achieved little success, we naturally were interested in the results of this study and wanted to make several observations. First, we learned as we were performing our trial that gestational age is a more ephemeral measurement than we initially believed.[1] We found that whereas the apparent gestational age distribution changed over time predominantly because of changes in the use of ultrasonography, the birth weight distribution and mean birth weight did not change. Because one possible explanation for the reported improvement in the preterm delivery rate over time is a change in the definition of gestational age, we would be interested to know, first, how the gestational age was determined, and second, what happened to the birth weight distribution over the time of their study?

It is, of course, encouraging to see a decrease in neonatal mortality over time. However, whereas the results are statistically significant there may be potential for bias in the results. For example, even though the authors admitted patients to the project at 20 weeks' gestation, which is equivalent to about 350 gm fetal weight, they nonetheless defined a neonatal death as those beginning at 500 gm, equivalent to about 23 or 24 weeks gestational age. Therefore the lower tail of potential mortality was excluded.

In addition, the authors do not present the neonatal mortality for the entire population studied, but only for those babies that by their definition were preterm. It would be interesting to know the neonatal mortality for the entire population admitted to the study and to see how this changed over time. In any case, neonatal mortality has improved over time in many institutions even when the preterm delivery rate did not. As an example, in the Mueller-Heubach article the neonatal mortality showed as large an improvement in the first year of the study, before any improvement in the preterm delivery rate, as occurred in subsequent years when the reported preterm delivery rate was lower.

However, even if the preterm delivery rate did change over time and the neonatal mortality improved, it is interesting to speculate what in the program may have led to these results. The authors state that the reason they believe the preterm delivery rate improved over time was that the method to be tested (i.e., risk screening, weekly evaluation, teaching) was adopted widely throughout their system. It is not clear from the methods section, but when the authors state that their entire prenatal system adopted the preterm prevention method, does this mean that the entire system went to a weekly visit with pelvic examinations and that this approach was applied to both high-risk controls and to their low-risk patients? This should be quantifiable and we would be interested in seeing these numbers. However, if that did not happen, the authors' statement about similarity in care between the high-risk treatment and all other groups should not be casually accepted because the difference in care between groups is important. For example, if the high-risk control and low-risk groups did not have weekly visits with examinations, it seems unlikely that the weekly visits and the weekly pelvic examinations played a significant role in the reduction in preterm delivery.

In regard to screening, inasmuch as nearly two thirds of the preterm deliveries came from the low-risk group, our calculations suggest that a substantial part of the improvement in the preterm delivery rate must have come from the low-risk population. If substantial improvement did occur in the low-risk group, then it seems safe to assume that screening for high-risk status was probably not of much value in producing the improvement. Also, because there was no significant difference in outcome between the high-risk treatment and control groups, it also appears that it is of little value to actually classify patients and move them into a high-risk group.

Because it seems that neither the screening, nor the classification, nor the weekly visits, nor the weekly pelvic examinations are plausible explanations or even necessary components for the improvement over time, it is not apparent to us which components of the program may have been responsible for its success. Certainly none of these program components is likely to be responsible for the reduction in the *diagnosis* of preterm labor, especially because the entire program was designed not to reduce the incidence of preterm labor, but to diagnose it early and treat it appropriately.[2]

Finally, we would like to remind the readers that the primary hypothesis and the study design involved a randomized trial of a specific intervention. This study design failed to show any benefit. In fact, although not statistically significant, the treatment group had a worse outcome (with a preterm delivery rate of 22.1% in the intervention group and 20.8% in the control group). This was also true in Philadelphia in a study by Main et al.[3] and in our part of the multicenter trial in Alabama.[4] It seems to us that what is important in this study is the result of the randomized trial, and its failure should not be so casually explained. Again, the Mueller-Heubach article and the Main[3] article, the only two randomized trials of this method of prematurity prevention that are now in print, failed to show any difference between the treatment and the control group. Certainly the authors did not prove that "the preterm birth rate . . . could be markedly decreased as a result of medical provider and patient education" nor did they show "that an intensive educational program among patients and providers can have a marked impact on the frequency of preterm birth." It is important to reread the title of this paper—"Preterm birth prevention: Evaluation of a prospective controlled, randomized trial." The results were negative. Any other interpretation, we believe, is misleading.

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Conclusions lack support

To the Editors:

After reading E. Mueller-Heubach et al.'s article, (Mueller-Heubach E, Reddick D, Barnett B, Bente R. Preterm birth prevention: evaluation of a prospective controlled randomized trial. AM J OBSTET GYNECOL 1989;160:1172-8), my evaluation of their study was very different from theirs. The authors concluded that "we were able to demonstrate that an intensive educational program . . . can have a marked impact on the frequency of preterm birth." I found no support in their article for this conclusion.

The authors assumed that the general change in attitude of medical personnel explains the lack of difference in preterm births between the intervention and the control groups. Were the controls seen weekly from 22 to 37 weeks' gestation as was the intervention group, and did they have weekly cervical examinations? Did the controls have the same intensive teaching with regard to symptoms and signs of preterm labor as did the intervention group? Were the amounts of rest, cessation of smoking, and use of tocolysis the same in both groups? From the description in the methods section, the answer has to be no! Yet, as noted, the authors did not find a difference in preterm births between the control and intervention groups. Does this mean that

none of these intervention techniques is important? A possible answer to the findings of this most unique "prospective controlled randomized trial" is that during the time of the study the socioeconomic status of their entire clinic population changed to be more like that of the private population.

In attempting to reduce the prematurity rate in Denver in pregnant clinic populations, our success has been limited by the noncompliant patient, by the users of street drugs, and by those patients who have no message telephone. In addition, the authors did not mention how gestational age was estimated. We now seem to have more mature small-for-gestational-age newborns (as judged by nursery personnel) than in the past, which improves our rate of premature births. In contrast to this bleak record, Hispanic patients appear to be reducing their rates of premature births. Is it possible that these detrimental factors do not operate in Pittsburgh? What was the outcome in the authors' "refuser" group? Perhaps this group can solve the puzzle of why the controls did so well.

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Reply

To the Editors:

We appreciate the comments of Goodlin as well as Goldenberg et al. with regard to our article. In response we would like to reemphasize the comment in our article that "we noted that the change in attitude of the medical personnel toward this preterm birth prevention program defeated the controlled randomized design of the study because management of the control group was not the same as it would have been before the onset of the study." For this reason, we titled our article "evaluation" rather than "results" of a prospective controlled randomized trial. As a result of our educational sessions, medical providers on their own began to give more instruction about preterm labor to patients irrespective of their risk assignment. We thought that it would be unethical and probably futile to ask medical providers not to do this, whereas we fully realized that our results would not be those of a prospective controlled randomized trial. Cervical examinations in patients not in the high-risk intervention group may have been more frequent but certainly were not done weekly, and we must conclude that weekly cervical examination did not contribute to the decrease in preterm birth rate. As we have pointed out, the decrease in preterm birth rate over time was a result of fewer patients first seen in preterm labor rather than more patients in preterm labor first seen as candidates for tocolysis.

With respect to determination of gestational age we used last menstrual period, size of uterus at early examination, quickening, and other clinical information. In cases of uncertainty and discrepancy early ultrasonographic examination was done and gestational age was adjusted when there was a ≥2-week discrepancy. Gestational age estimates were verified after delivery by Dubowitz scoring by the pediatrician. In contrast to Goldenberg et al. we have not changed our ultrasonic measurement techniques of the fetus during our study and thus have been spared the difficulty that they had in their preterm birth prevention study. We agree with Goldenberg et al. that on the basis of our results, screening for high-risk status is of limited value. In turn we suggest education of all pregnant patients about subtle symptoms and signs of preterm labor, uterine palpation and rest, and self-hydration when more than occasional uterine activity is noted.

We are aware that others have not observed a decrease in preterm birth rate in preterm birth prevention studies. This may be because of differences in patient population as suggested by Goodlin. Recent analysis of our study population by race revealed a very significant decrease in preterm births ($p < 0.001$) in 2446 white indigent patients in year 2 and 3 of the study with preterm birth rates lower than those in our white private population. In contrast, in 2599 black indigent study patients the preterm birth rate decreased much more modestly, reaching statistical significance ($p < 0.01$) only in year 3 of the study despite particular efforts to communicate with our black study population. It appears from our results that preterm birth prevention studies that involve predominantly black indigent patient populations and small sample sizes are not likely to show significant changes in preterm birth rate.

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Volume and timing are key to use of intraumbilical oxytocin for management of retained placenta

To the Editors:

I read with great interest the article by Reddy and Carey (Reddy VV, Carey JC. Effect of umbilical vein oxytocin on puerperal blood loss and length of the third stage of labor. Am J Obstet Gynecol 1989;160: 206-8).

As they state in the Comment section, some controversy concerning the value of intraumbilical injection of oxytocin for the management of the third stage of labor or for the retained placenta does indeed exist.

As for the routine use of oxytocin in the management of the third stage of labor, the above study clearly shows in a randomized controlled manner that this maneuver shortens the length of the third stage of labor and diminishes blood loss. This confirms a previous observation, although uncontrolled, by Neri et al.[1] I definitely agree with their conclusion that this management

is a useful alternative to the traditional management of the third stage of labor, especially when fluid intake should be restricted or blood loss minimized.

As for the use of intraumbilical oxytocin for the management of the retained placenta, despite few reports that do not claim an advantage of the procedure,[2-4] I have no doubt in my mind that the properly timed intraumbilical injection of oxytocin is of great value in the management of the retained placenta.

Chestnut et al.[2] injected intraumbilical oxytocin if the placenta was not expelled in 5 minutes, which obviously is too short of an interval. Kristiansen et al.[3] have waited 20 minutes, which might still be too short of a waiting period before intervention. These authors have also used a smaller volume (10 ml) for the intraumbilical injection, which I believe is not enough to overcome the "dead space" in the umbilical cord and the placental vasculature. The hydraulic effect of the injected solution has its merits as it may in itself enhance placental separation by changing placental uterine interrelations. This principle was the basis for the Majon Gabastou maneuver, intraumbilical injection of 200 to 250 ml of physiologic solution, which was popular in the early 1930s in Europe when placental separation was delayed.[1] Haukson et al.[4] have waited as long as 60 minutes before intervention. It is possible that by increasing the waiting period some placentas otherwise defined as "retained" would be delivered. The 60-minute wait could have preselected the especially difficult cases (placenta accreta or increta), which could account for the relatively lower success rate (46%) and the reported longer injection-expulsion interval supports this assumption.

We all know that it was common practice in earlier days to wait an hour or even longer. However, today it is considered unwise to wait that long, exposing the parturient to the risks of increased third-stage blood loss and subsequent puerperal anemia. The risks of puerperal infections related to anemia and to puerperal blood transfusions should be continuously kept in mind.

Even in Kirstiansen's study 40% to 42% of the retained placentas could have avoided manual lysis under general anesthesia, which usually is the traditional management.[5]

In our hands the intraumbilical injection of oxytocin seems to be a very effective, quick, and safe method for the separation and delivery of the retained placenta. It has been successful in avoiding manual lysis under general anesthesia in more than 70% of cases.[5-7] I believe that oxytocin applied in this manner reaches the partially disrupted placental bed in a relatively higher concentration, stimulating uterine contraction and enhancing the cleavage of the placenta at the decidua spongiosa level. The hematoma that forms in this area further accelerates the process, and the placenta eventually separates and is delivered.

It seems that the injected solution may also have an hydraulic effect and may in itself contribute to placental separation by mechanical pressure as with the injection of saline solution alone. Thus the volume of the injected solution is of considerable importance. The timing of intervention is also of critical importance. It should not be too early and should not be unnecessarily delayed. I believe that the recommended waiting interval should be neither more nor less than 30 minutes. No maternal ill effects were reported even by the method's objectors, so why not use it when there is a chance to avoid manual lysis and general anesthesia, even if the success rate is not as high as in our experience?

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Response declined

Effects of selection bias on outcomes at referral centers

To the Editors:

Lubchenco et al. (Lubchenco LO, Butterfield LJ, Delaney-Black V, Goldson E, Koops BL, Lazotte DC. Outcome of very-low-birth-weight infants: Does antepartum versus neonatal referral have a better impact on mortality, morbidity, or long-term outcome? AM J OBSTET GYNECOL 1989;160:539-45) concluded that the better place to deliver a newborn weighing 500 to 1499 gm is a tertiary care referral center. They reported fewer fetal deaths, less neonatal morbidity, possibly a lower neonatal mortality, and better long-term outcome, when compared with results at the surrounding level I community hospitals. But their claims have been derived from a selected population at their referral center, not a stochastic one, as they have inferred by calling their study a total population-based one.

The authors were well aware of selection biases that distort reports of outcome at referral centers. All new-

borns delivered outside the center and who were referred in for care were excluded. This is a bias that can spuriously reduce mortality rates among very small newborns.[1] Furthermore, they have excluded all mothers who were transferred antenatally to the center for care, a source of selection bias that is controversial.

After these known sources of bias are excluded, a substantial distortion in the birth weight distribution of the infants remains. There were approximately 10,000 deliveries in the 4-year period under investigation.[2, 3] One half of these deliveries were excluded because the mothers were transferred antenatally for management of complications of pregnancy or impending problems of labor. Therefore the incidence rate of infants weighing 500 to 1499 gm in this study (145 infants born alive) was 2.9% or almost three times greater than the rate of a random distribution of newborns in this weight group, for Colorado or the United States.[4] Moreover, the 37% nonwhite mothers at the referral center, if all were black, could not account for a very-low-birth-weight rate of this magnitude.[4]

A possible explanation for the evident patient selection, suggested by Paneth et al.[5] but not investigated, is self-selection by the patients themselves. Referral centers have done their share of advertising; their existence in the community is advertisement itself. Women who anticipated very-low-birth-weight infant problems may have sought out the referral hospital. They also may have been better risks and better-motivated patients than the women in the general population. The subtleties of self-selection and motivation could be too elusive for statistical analysis. Nevertheless, the explanation is plausible too and should not be dismissed for the lack of quantifiable information.[6]

There remains a dimension of concern, perhaps more basic to perinatology. Reports from this particular referral center have served as a source of widely recognized reference data for predicting neonatal mortality rates in relation to birth weight and gestational age.[2, 7] The information and graphics in these reports have also been derived from a selected population, not an area-based, random population. Furthermore, as the rates of birth under 1500 gm increased from 2.3% of live births (1958 to 1968) to 3.9% of live births (1974 to 1980), indicating increased patient selection and potential selection bias, the mortality rate of this weight group declined. Antenatal transfers to the referral hospital also were included in these reports.

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Reply

To the Editors:

Dr. Sepkowitz has addressed the numerous problems encountered in clinical research. Try as one can to control for variables, unexpected ones arise. Such was the case in this project when we discovered the large number of infants with birth weights of 500 to 1500 gm born to mothers who were transferred to the University of Colorado Health Science Center (UCHSC) for delivery because of obstetric problems.

Dr. Sepkowitz is quite astute in comparing our article with previously published data from our unit (his references 2 and 7). It gives me special pleasure to know that sufficient detail was presented in these publications to permit the comparisons and address the questions that he raised.

First of all, I wish to clarify a statement made in his opening paragraph. He writes that our data reported "possibly a lower neonatal mortality and better long-term outcome . . ." for infants born in the tertiary center. We did report that neonatal mortality was improved only in the *smallest* infants (i.e., <700 gm). There were *no* differences in overall long-term handicaps among the two populations.

The article by Koops et al. (his reference 2) gives mortality data on births at the University of Colorado Health Science Center over a 6-year period, from July 1974 to July 1980, to document the improved survival of infants in every birth weight and gestational age group. These data overlap the material published in our article, January 1975 through December 1978. Our article deals only with birth weights of 500 to 1500 gm while Koops' paper includes all births. The crucial piece of information that is lacking in the Koops data and ours is the birth weight distribution of infants born to the high-risk mothers referred to UCHSC for delivery.

I will attempt to provide this missing link from the figures available since Dr. Sepkowitz' figures and mine do not agree.

In paragraph 3, he notes (from Koops et al.) that there were approximately 10,000 deliveries during the 4-year period that we studied. This is correct. Then he states that "one half of these deliveries were excluded because the mothers were transferred antenatally for management of complications. . . ." This is not correct—*we* excluded half of the infants with birth weights 500 to 1500 gm because we knew that they were

Table I. Comparison of three reports by live births per year

	Lubchenco et al. (1972)	*Koops et al. (1982)*	*Lubchenco et al. (1989)*
Time of study (yr)	1958-1968	1974-1980	1975-1978
Population	All births; no maternal referrals	All births	Births 500-1500 gm; no maternal referrals
Length of study (yr)	10	6	4
Live births			
No.	16,287	14,413→	9,608 (based on 4 of 6 yr)
No./yr	1,629	2,402→	2,402
Births 500-1500 gm			
Total	298	538	145
No./yr	30 (1.84%)	90 (3.75%)	36 (1.5%*)

*If an equal number of infants from maternal transports were added to the 145 clinic live births (n = 290), the incidence of very low birth weight would be 3.0%.

maternal referrals. Only 5% of the 10,000 births in Koops' article were from maternal transfers. Koops et al. state that there was an increase in referral of high-risk mothers to the tertiary center "from 60 in 1974 to more than 150 in 1980."

I have expressed the numbers and percentages in live births per year from the three articles to which Dr. Sepkowitz refers (Table I).

A total of 5% of Koops' population of high-risk mothers would produce approximately 120 live-born infants per year. If the incidence of very low birth weight in the clinic population remained constant at 1.84%, as in 1958 to 1968, one would expect 44 infants on the basis of the increased number of deliveries. It is possible, and likely, that ≥46 of the 120 infants born to high-risk mothers would weigh between 500 and 1500 gm, giving an incidence in the UCHSC population of 1.91%.

Additional unpublished data show a rather constant number of births at UCHSC per year with birth weights 500 to 1500 gm up to 1973 and 1974 (n = 27 to 33 per year) during the years when few high-risk mothers were referred to UCHSC for delivery. In 1973 and 1974 the number of infants with very low birth weight more than doubled, to 75, and continued to rise, to 112, in 1979.

These figures do not support a global increase or a local increase in very low birth weight but, in my opinion, suggest an increased awareness of maternal high-risk problems and referral of mothers to tertiary centers for delivery of these infants.

There may be an effect on neonatal mortality when infants born to high-risk mothers are included. In fact, there was a slight but significant improvement in neonatal mortality in the referred group in our study (25% vs 37%).

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Functional tolerance to the effects of ethanol on fetal biophysical activities?

To the Editors:

We read with great interest the case report by Castillo et al. (Castillo RA, Devoe LD, Ruedrich DA, Gardner P. The effects of acute alcohol intoxication on biophysical activities: a case report. Am J Obstet Gynecol 1989;160:692-3) concerning the effects of alcohol (ethanol) intoxication on fetal biophysical activities at 37 weeks' gestation. It is fascinating that fetal breathing activity persisted at near-normal levels when the maternal blood ethanol concentration was 322 mg/dl. The authors reported that the mother was admitted to the hospital on two previous occasions during this pregnancy for management of acute ethanol intoxication with similar maternal blood ethanol concentrations. The neonatal examination revealed facial anomalies consistent with the craniofacial dysmorphology of the fetal alcohol syndrome. These findings collectively are indicative of chronic maternal ingestion of excessive amounts of ethanol during gestation.

The pattern of fetal biophysical activities reported by Castillo et al. differs from the profile that we previously reported for maternal ingestion of a single, low dose of ethanol.[1] In our study of healthy pregnant women at 37 to 40 weeks' gestation, fetal breathing movements were virtually abolished by 30 minutes when the maternal blood ethanol concentration was maximal (33 mg/dl) and remained abolished for 3 hours, at which time maternal blood ethanol concentration was virtually nonmeasurable. This apparent discrepancy in the effects of ethanol on fetal breathing activity may be a result of the development of functional tolerance after repeated maternal consumption of ethanol.

We published the results of a study of near-term fetal sheep that showed that short-term maternal administration of moderate-dose ethanol resulted in the development of functional tolerance to the ethanol-induced suppression of fetal electrocortical and electroocular activities (after 7 days) and fetal breathing movements (after 14 days).[2] These findings are consistent with the observations in the case study of Castillo et al. However, the mechanism by which the mature fetus develops functional tolerance is not known.

In view of the fact that tolerance and physical dependence can develop in the adult during chronic ingestion of ethanol, it would be of interest to know whether the authors observed any withdrawal symptoms, including increased breathing activity, in the neonate. In this regard, it is noteworthy that the authors reported more than a twofold increase in breathing

incidence in the fetus when the maternal blood ethanol concentration decreased to <10 mg/dl; this is indicative of ethanol withdrawal in the fetus.

The authors speculate that their findings with regard to fetal breathing activity may have resulted from a transient metabolic acidosis or increased central nervous system levels of carbon dioxide in the fetus as a consequence of the acute ethanol intoxication. We have examined the effect of maternal administration of acute, high-dose ethanol on maternal and fetal arterial blood gases and acid-base balance in the near-term pregnant sheep.[3] There were no measurable changes in maternal and fetal blood gases and acid-base balance even at maternal and fetal arterial blood ethanol concentrations of 374 mg/dl and 382 mg/dl, respectively. On the basis of these data, it appears unlikely that a fetal acidosis occurred in the case reported by Castillo et al. Furthermore, to speculate that a transient fetal metabolic acidosis or increased central nervous system levels of carbon dioxide may have existed as a result of the metabolism of acetaldehyde, the proximate metabolite of ethanol, is scientifically incorrect. Acetaldehyde oxidation, catalyzed primarily by hepatic aldehyde dehydrogenase, leads to the formation of acetate. Increased reducing equivalents in the liver (i.e., nicotinamide adenine dinucleotide phosphate) and consequent reduction of pyruvate to lactate would have to occur to produce metabolic acidosis, and acetate would have to be oxidized by means of intermediary metabolism (i.e., tricarboxylic acid cycle) to produce carbon dioxide. Also, it has been well established that although maternal and fetal blood ethanol concentrations are virtually identical, the maternal and fetal blood acetaldehyde concentrations are about 1000-fold less than the respective ethanol concentrations, and the acetaldehyde concentration in fetal blood is less than that in maternal blood.[4,5] These pharmacokinetic data indicate that acetaldehyde has a minor role at best in the effects of maternal ethanol ingestion on the fetus.

These comments are intended to complement, not to detract from, the findings of this very interesting case report and especially the final conclusion drawn by the authors—that it is important to document maternal ethanol consumption when fetal biophysical activities are to be evaluated.

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Reply

To the Editors:

We appreciate the interest of Drs. Smith, Patrick, and Brien in our case report, especially because their work on the effects of alcohol on the fetus is well known. With regard to the postnatal behavior, there was nothing noted in the baby's chart at birth to suggest withdrawal symptoms. The vital signs were stable and the overall behavior during the first 48 hours after birth was unremarkable.

With respect to the possible mechanisms responsible for the observed responses, it is interesting that although the authors of the letter find our theory scientifically invalid, reference 4 of their letter states that acute high-dose intake of alcohol can cause a transient collapse in the umbilical vasculature, resulting in fetal hypoxia and acidosis. Also, low levels of acetaldehyde in the fetal sheep circulation is not conclusive proof that acetaldehyde or its metabolites may not have a role in the pathogenesis of abnormal responses in the human fetus. Whereas tolerance to alcohol is a good explanation, the presence of fetal tachypnea and complete absence of fetal heart rate variability point toward an overall abnormal fetal response and not to an adaptive mechanism.

We look forward to the continuing work from this group of investigators in this area in which very little is known.

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Blood sampling and transfusion in utero suggested in the pumping twin

To the Editors:

We read with great interest the article by Stiller et al. (Stiller RJ, Romero R, Pace S, Hobbins JC. Prenatal identification of twin reversed arterial perfusion syn-

drome in the first trimester. AM J OBSTET GYNECOL 1989;160:1194-6). Repeated ultrasonographic evaluation failed to reveal any sign of fetal congestive heart failure. Thus, the cord hemoglobin was 8.5 mg/dl at delivery and the infant died 3 days after birth. Unfortunately, the cause of death was not given. In accordance with the range of fetal hemoglobin concentration,[1] this fetus suffered from moderate anemia.

Van Allan et al.,[2] who reported the largest series of reversed arterial perfusion syndrome, noted that the main cause of morbidity and mortality of the pumping twin was congestive heart failure. Failure of ultrasonographic parameters to predict the severity of the anemia in rhesus isoimmunization was recently reported and fetal blood sampling was suggested in these cases.[3]

In light of this information we suggest that blood sampling of the pumping fetus should be taken and blood transfusion should be performed in utero if indicated to prevent fetal anemia and congestive heart failure.

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Reply

To the Editors:

We appreciate the comments related to our article. It was suggested that fetal blood sampling be performed in the pump twin to assess for fetal anemia, with intrauterine transfusions to be performed if needed.

Unfortunately, little information exists in the literature as to the incidence of fetal anemia in twin reversed arterial perfusion pump babies. In the Van Allen et al. series of 14 pregnancies complicated by twin reversed arterial perfusion, no hemoglobin information is available.[1] A central question is whether the congestive heart failure that often occurs in pump fetuses is a result of the cardiovascular demands of supporting two circulations or whether it is a result of anemia.

Given the limited information concerning the fetal cardiovascular hemodynamics of the twin reversed arterial perfusion syndrome, the suggestion to perform fetal blood sampling is not unreasonable. It is hoped that further studies will document the value or lack there of in the management of this problem.

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Lichen sclerosus, invasive squamous cell carcinoma, and human papillomavirus

To the Editors:

Invasive squamous cell carcinoma of the vulva appears to arise in association with a coexistent intraepithelial abnormality.[1] This abnormality usually falls into two main categories, either hyperplastic dystrophy, associated with lichen sclerosus in most cases, or severe atypia grade 3 (vulvar intraepithelial neoplasia). Controversy exists over the malignant potential of lichen sclerosus, with studies demonstrating the coexistence of lichen sclerosus in excision specimens of squamous cell carcinoma ranging from little or no association[2] to 63%.[3] In our own series of 78 cases of squamous cell carcinoma the histologic coexistence with lichen sclerosus was 60%. Conversely, however, in clinical practice this relationship is small as we examine and treat a large number of patients with lichen sclerosus, few of whom subsequently develop a squamous cell carcinoma.[3, 4] This discrepancy may reflect the beneficial effects of treatment as the majority of cases of lichen sclerosus recognized histologically in the squamous cell carcinoma specimens had not been diagnosed or treated previously. Alternatively, the difference may indicate the prerequisite of a cofactor such as concurrent infection with human papillomavirus (HPV). To test this hypothesis we analyze 10 cases of squamous cell carcinoma with coexistent lichen sclerosus to determine the presence of HPV. The technique used for detection of the virus was Southern blot hybridization under stringent conditions. Table I indicates the probes used and the results.

The negative findings suggest either that the viral deoxyribonucleic acid tested was not present or that insufficient total deoxyribonucleic acid was available for detection in the tissues sampled. The latter explanation seems unlikely as we had conducted simultaneously an analysis with the same technique on 10 cases of squamous cell carcinoma with evidence of grade 3 vulvar intraepithelial neoplasia; we obtained positive results in seven of the 11 lesions (Lessana-Leibowitch M. Unpublished data), and in six of seven HPV #16 was detected.

Table I. HPV deoxyribonucleic acid sequences in squamous cell carcinoma of vulva with coexistent lichen sclerosus

Probe	*Detection*
HPV 16	0/10
HPV 18	0/10
HPV 31	0/10
HPV 33	0/10
HPV*	0/10

*Undetermined type.

A recent study of five cases of uncomplicated lichen sclerosus failed to demonstrate the presence of HPV.[5] These preliminary results suggest that HPV is not implicated in the etiology of lichen sclerosus or in the induction of malignant change in this disorder.

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The Southern blotting was kindly performed in the virology laboratory of the Pasteur Institute, Paris, under the supervision of Professeur Gerard Orth.

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Measurement of unconjugated estriol by enzyme-linked immunosorbent assay fails to show an association with Down syndrome

To the Editors:

Canick et al.[1] and subsequently Wald et al.[2] have reported on the use of unconjugated estriol as a marker for Down syndrome in a protocol of prenatal maternal serum screening. Their reports indicate that maternal serum levels of unconjugated estriol are significantly lower in pregnancies affected by Down syndrome than in matched controls. Any marker that adds to detection efficiency in prenatal Down syndrome screening, would be particularly welcome. The poor performance of maternal serum α-fetoprotein as a marker for Down syndrome has been reported.[3-5]

Table I. Levels of unconjugated estriol in 27 cases of trisomy 21

Rank	*Gestational age (wk)*	*MoM*
1	18	0.4
2	18	0.4
3	16	0.64
4	17	0.64
5	15	0.68
6	15	0.68
7	15	0.69
8	17	0.8
9	14	0.82
10	16	0.86
11	16	0.87
12	16	0.95
13	17	1.04
14	15	1.09
15	15	1.1
16	16	1.15
17	18	1.15
18	15	1.16
19	16	1.39
20	18	1.51
21	16	1.82
22	16	2.31
23	16	2.47
24	16	2.57
25	15	2.8
26	16	2.94
27	16	3.79

Table II. Percent of Down syndrome cases and controls with maternal serum unconjugated estriol levels less than or equal to given MoM levels

Unconjugated estriol level (MoM)	*Down syndrome cases (%)*	*Controls (%)*
≤0.50	7.4	4.7
≤0.65	14.8	19.4
≤0.80	29.6	36.5
≤1.00	44.4	51.3

Our first evaluation[6] of unconjugated estriol used the same radioimmunoassay reagents and procedure (modified per Canick et al.[1] and Wald et al.[2]), but did not show the utility of this marker. No significant difference was found in the level of unconjugated estriol between controls and pregnancies affected by Down syndrome.

We have completed a further study of unconjugated estriol with the use of a different method of measure-

ment, enzyme-linked immunosorbent assay (ELISA). Table I shows unconjugated estriol values as determined by ELISA in 27 documented cases of trisomy 21 relative to 515 controls matched for gestational age, maternal age, and freezer storage time. In addition, all samples were from white, nondiabetic, singleton pregnancies. This second study does not show a reduction in the level of unconjugated estriol in Down syndrome cases. Indeed, on average, the unconjugated estriol value in Down syndrome cases (median multiple of the median [MoM]* = 1.09) is higher than in controls (median MoM = 0.99). This data is particularly striking in light of the fact that levels of unconjugated estriol in controls, established with ELISA, range from 1.2 to 2.5 ng/ml during weeks 14 to 18 of gestation and are similar to radioimmunoassay data previously reported during this stage of pregnancy. Table II shows that the distributions of maternal serum unconjugated estriol levels in pregnancies affected by Down syndrome and controls overlap to such a degree that discrimination becomes impractical.

The results of this study suggest that maternal serum unconjugated estriol evaluation by ELISA as an additional marker in a Down syndrome screening protocol will reduce detection efficiency because the unexpected higher levels of this analyte in cases of Down syndrome would artificially reduce risk. The fact that unconjugated estriol when measured by different clinical laboratory techniques fluctuates about 1 MoM in Down syndrome cases provides no support for the hypothesis that the unconjugated estriol analyte is a marker for Down syndrome. We recommend against the use of unconjugated estriol within a prenatal Down syndrome screening protocol.

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*We note that multiple of the median as a statistical parameter of measurement is appropriate but multiples of the median should not be used for reporting to clinicians or patients.[3]

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Fructosamine in gestational diabetes

To the Editors:

We read with great interest the article by R. Comtois et al. (Comtois R, Desjarlais F, Nguyen M, Beauregard H. Clinical usefulness of estimation of serum fructosamine concentration as screening test for gestational diabetes. AM J OBSTET GYNECOL 1989;160:651-4).

Glycosylated serum proteins, measured as fructosamine, have been used for several years as an index of short-term control of diabetes mellitus, often in conjunction with glycosylated hemoglobin, which measures medium to longer-term control.

In the diagnosis and management of gestational diabetes it is essential to have an index of short-term hyperglycemia because this condition may not develop until late in pregnancy. Roberts et al.[1,2] have proposed that fructosamine can be used as a screening test for gestational diabetes and on theoretic grounds this would seem to have some distinct attractions, particularly because that fructosamine should reflect the extent of hyperglycemia in patients on their normal diet rather than under the very artificial conditions of a glucose tolerance test (GTT).

To examine this proposition we examined the relationship between serum fructosamine and GTT results in 161 successive patients given GTTs at 30 weeks' gestation. These patients were selected for a GTT on the basis of a screening test given to all antenatal patients. Positive screening test results consisted of a plasma glucose level >8.1 mmol/L 1 hour after a 75 gm glucose load taken in the nonfasting state at 28 weeks' gestation.

The GTT procedure consisted of capillary whole blood glucose measurement (YSI glucose analyzer, Yellow Springs Instrument Co., Yellow Springs, Ohio) before, 1 hour after, and 2 hours after ingestion of a 100 gm load taken after an overnight fast. The criteria for an abnormal glucose value were fasting >5.0, 1 hour >9.5, and 2 hour >8.1 mmol/L. Fructosamine was also measured on the fasting sample with the Roche kit on a Cobas FARA analyzer (F. Hoffmann-La Roche Ltd., Basel). The between batch precision was 3% and 6% at levels of 1.72 and 3.50 mmol/L, respectively.

The results shown in Table I indicate that there is no significant difference in fructosamine levels in women with gestational diabetes, as compared with normal women. This result indicates that serum fructosamine is of no value in either the diagnosis or the monitoring of management of diabetes in pregnancy.

Table I. Fructosamine levels in relation to oral GTT

Results	No.	Fructosamine (mmol/L)		p Value
		Mean	SD	
Normal	116	2.04	0.19	—
Elevated				
1 hour only	13	2.06	0.21	>0.7
2 hours only	9	2.02	0.12	>0.8
1 and 2 hours	23	2.07	0.28	>0.4

abetes by the week 30 of pregnancy may reflect the mildness of the hyperglycemia in this condition and the shortness of duration of the glucose intolerance.

These results are very similar to those reported by Comtois et al. desite the fact that they were reporting on patients examined because of clinical risk of gestational diabetes, whereas our study looked at a group selected on the basis of a screening test applied to a total antenatal population.

Therefore the situation remains that until some better test is available the only reliable method to detect patients at risk of gestational hyperglycemia is to perform an oral GTT at 28 to 30 weeks' gestation.

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Reply

To the Editors:

We are pleased to see that Doery et al. were interested in our article and even performed a study of the clinical usefulness of serum fructosamine as a screening test for the total antenatal population.

The results observed by Doery et al. are similar to ours, despite the fact that the fructosamine screening test was applied in a "less selected" population. However, the study did not report the results on their pregnant patients of serum fructosamine levels corrected for the protein concentration, which according to our data improves the sensitivity of this test.

In our study the difference between the serum fructosamine concentrations of the women with gestational diabetes and the pregnant women with normal glucose tolerance test results, even when expressed in a more sensitive form such as the fructosamine/protein ratio (39 ± 3.9 μmol/gm versus 37 ± 3.2 μmol/gm, $p < 0.05$), was statistically less significant than the difference between their fasting serum glucose levels (107 ± 13.7 mg/dl versus 82 ± 8.6 mg/dl, $p < 0.001$). The first explanation is that the sensitivity of fructosamine is too low to detect a difference in the mean daily blood glucose level of approximately 30 mg/dl between the two groups. In our study the mean daily blood glucose level of our patients with gestational diabetes was 122 ± 27 mg/dl. These results also could be explained, at least in part, by the fact that during the few weeks before the diagnosis the usual mean glucose level in patients with gestational diabetes on spontaneous diet was just slightly higher than that in normal pregnancy; consequently, the increase in fructosamine level was usually not large enough to be clinically useful. Another explanation could be that patients with gestational diabetes had a lower caloric intake than that of normal pregnant patients. Because we observed a good correlation between serum fructosamine/protein ratio and spontaneous caloric intake ($r = 0.72$, $p < 0.005$), the fructosamine level of the patients with gestational diabetes could be relatively decreased by this lower caloric intake. However, additional studies that quantify more precisely the spontaneous diet in normal pregnant patients and in patients with gestational diabetes are needed before any definitive conclusions can be drawn about the results of a possible difference in the spontaneous diet of these two groups of patients with regard to fructosamine levels.

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Blood gas studies in fetal heart blood

To the Editors:

I enjoyed the article by Westgren et al. (Westgren M, Selbing A, Stangenberg M, Phillips R. Acid-base status in fetal heart blood in erythroblastotic fetuses: a study with special reference to the effect of transfusions with adult blood. AM J OBSTET GYNECOL 1989;160:1134-8) and note that several of the changes they report in fetal

blood gas and acid-base status in response to anemia and transfusion of adult blood were similar to our findings.[1, 2] However, their use of blood obtained from the fetal heart and imperfect statistical analysis may explain the differences from our results.

Fetal heart blood is a mixture of blood from the ductus venosus, upper and lower parts of the body in descending order of oxygenation. Streaming of blood within the heart is thought to minimize mixing and so the blood gas results would depend on the exact site of sampling, even within a chamber of the heart. Their statement "the primary target for the puncture was the left ventricle" suggests that sometimes the blood was obtained from other chambers. Therefore, at the very least they need to publish control data for heart blood from fetuses without erythroblastosis. As they state in the article they also need to investigate changes with gestational age because these are important in cord blood[3] and our data analysis corrected for this factor.

Westgren et al. found no fall in pH or rise in base excess in the heart when fetuses had adult blood in their circulation, whereas our study found these changes in umbilical arterial blood. The most likely explanation for this difference is that heart blood is a mixture of umbilical arterial and venous blood so abnormalities we found in the former were not detected.

Finally, their data were 70 observations from 26 fetuses, whereas ours were 80 observations from 80 fetuses. This means that they included multiple observations from some pregnancies and the data were not independent as required for multivariate analysis.

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Reply

To the Editors:

We wish to refute the challenge of Dr. Soothill that the difference between our results and theirs is because of "imperfect statistical analysis." Before use of a multivariate analysis, stratification was performed for dependent observations in our study so the statistical analysis does not explain the discrepancy between our two studies.

A more likely explanation is that different sites were used to obtain fetal blood. We studied mixed venous and arterial blood, whereas Soothill et al. studied pure umbilical artery blood. It is not surprising that these two puncture sites differ in respect to studied parameters.

Finally, although the study by Soothill et al. included 80 observations, they based their analyses in respect to umbilical artery blood on 13 pairs, 26 observations, which is a rather limited number to achieve a high degree of confidence ($p < 0.036$).

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Active management of labor

To the Editors:

I have been studying active management of labor as described by O'Driscoll and Meagher[1] in connection with the preparation of my master's thesis in nursing at the University of Washington. I have just read the latest response by Leveno et al.[2] to O'Driscoll et al.[3] in the continuing repartee between Dallas and Dublin. A few thoughts and questions have occurred to me concerning the merits of the active management protocol, and the challenge to them put forth by Leveno et al.[2]

The effect that active management has on several of the outcome variables of labor has been measured by researchers among different populations. In Canada, Akoury et al.[4] compared a sample of 552 normal nulliparous women delivered of infants in accordance with the system of active management with 553 similar control subjects managed with routine care. Turner et al.[5] studied a multiracial sample of 1000 nulliparous patients whose labors were actively managed, and Sheehan[6] compared the records of 569 low-risk nulliparous patients from the National Maternity Center in Dublin, where active management is practiced, with 471 similar patients who were delivered of infants in a hospital in the United States. The findings of these three groups of investigators included decreased rate of cesarean section, length of labor, and rate of forceps delivery among the actively managed parturients, with no increase noted in perinatal morbidity or mortality. These results would indicate, as Turner et al.[5] stated, ". . . active management can be safely applied outside Ireland to reduce the incidence of Caesarean childbirth."

From a nursing perspective, other studies also add an interesting dimension to the active management debate. Research conducted by the pediatricians Klaus et al.[7] and Kennell et al.[8] has evaluated one component of active management, that of constant supportive companionship for the laboring patient. With no changes in medical care, these researchers have found in controlled, randomized trials that the constant presence of a reassuring female companion for the woman has produced statistically significant reductions in the rate of

cesarean section, duration of labor, and perinatal complications. Their results were comparable to the effects of active management of labor as measured by O'Driscoll and Meagher.[1] O'Driscoll and Meagher[1] have written, "Strict limitation of the duration of labor and continuous personal attention throughout are considered to be the basic requirements on which a high standard of care depends . . . neither is possible without the other." Could it be that the constant supportive and individualized nursing care practiced in active management is in large part responsible for its beneficial effects on the outcome of labor?

I await with interest the reply from Dublin to the report of Leveno et al.[2] If, after the results are in, active management does not fulfill its promises, this debate has at least encouraged a critical appraisal of the high cesarean section rate in the United States. Women in this country are perhaps due a reasoned and well researched justification for the frequent use of this procedure.

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This letter is a personal communication and is not intended to reflect the views of the University of Washington.

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Reply

To the Editors:

We are delighted with Nurse Lynch's letter concerning our report on cesarean section. Nurse Lynch correctly emphasizes that "constant supportive and individualized nursing care" is undoubtedly pivotal in good obstetric care. However, we are reluctant to broaden the cesarean rate debate to allegations about superiority (or inferiority) of nursing on two continents. Indeed, we are prepared to rise up for our own nurses!

We too are of the view that "women in this country are . . . due a reasoned and well researched justification of the frequent use of this procedure (cesarean)." We believe this sentiment has fueled our participation in the debate. Our purpose has not been to defend abuse of cesarean section but instead to encourage its prudent use.

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Subspecialty of gynecologic oncology proposed to manage breast disease

To the Editors:

I read with great interest the article by Dr. Norbert Gleicher (Gleicher N. Breast disease programs in obstetrics and gynecology: a plea for training in mammography. AM J OBSTET GYNECOL 1989;161:267-70). His point that the gynecologist most often faces breast disease and should be familiar with mammography is excellent. I would like to take his suggestion one step further.

It is disconcerting to the patient to be seen by different physicians for the detection, diagnosis, and treatment of breast disease. When a malignancy is detected, the patient is often treated not only by a surgeon but also by a medical oncologist and a radiotherapist. Inasmuch as the breast is a reproductive organ, I suggest that the subspecialty of gynecologic oncology have a role in the care of the patient with breast cancer. In this subspecialty the physician is trained in the detection of malignancy and coordinates the surgical, medical, and radiotherapeutic management. I believe this goal could be accomplished by incorporating training in the management of breast cancer into fellowship programs.

Although this concept would represent a major change in the present approach to women with breast cancer and will certainly encounter resistance and criticism, I suggest a pilot program be established at several centers to evaluate the role of the gynecologic oncologist in the treatment of this disease. Ultimately I believe the care of women will be improved by such action.

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Placental siderosis in maternal β-thalassemia

To the Editors:

Whereas the article by Birkenfeld and coworkers (Birkenfeld A, Mordel N, Okon E. Direct demonstration of iron in a term placenta in a case of β-thalassemia major. AM J OBSTET GYNECOL 1989;160:562-3) is of interest, such placental deposits of stainable iron have

long been recognized in the absence of maternal hemoglobinopathy. They form part of the spectrum of normal placental maturation and senescence from the ninth gestational week onward.[1] Basement-membrane siderosis alone, even in the setting of maternal β-thalassemia, is not necessarily a significant finding, and the statement of Birkenfeld and coworkers that "positive (iron) staining in the placental villi probably reflects tissue ferritin and hemosiderin deposits *that prevent excessive iron transport to the fetus*" (emphasis added) is not justified by the data presented.

Normal values for placental iron content[2] and for levels of iron, ferritin, and transferrin saturation in term infant umbilical cord blood[3] have been defined. Were placental concentrations of iron determined for the pregnancy in question? Was evidence of iron loading sought in the infant? These data might provide valuable information about the regulation of maternofetal iron transport in the presence of maternal hypersideremia.

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Reply

To the Editors:

We thank Dr. Knisely for his comments. Publications that describe transferrin and ferritin in the human placenta have applied immunohistochemical methods for the detection of these substances.[1,2,3] McKay et al.[4] have stated that "during the third trimester there is a progressive diminution in the amount of iron deposited in the placental stroma. The subtrophoblastic deposits noted in the second trimester have *all but disappeared.* A few villi in many term placentas however contain one to several *macrophages* (Hofbauer cells) which contain ferric but not ferrous iron."

We have used the Gomori Prussian blue reaction to detect hemosiderin in normal term placentas and were unable to visualize stainable iron in the stroma of the chorionic villi. However, we did show it in the term placenta from a mother suffering from β-thalassemia major.[5] It is known that with normal iron stores only trace amounts of hemosiderin are found in the body, mainly in reticuloendothelial cells in the bone marrow, spleen, and liver. In iron-overloaded cells, most of the iron is stored in the form of hemosiderin. The Prussian blue reaction that we have used might not visualize very small amounts of ferritin in the placental villi, whereas sensitive immunohistochemical methods will do so.

We believe that taken together, these observations do imply a difference of placental iron load between the normal placentas and the placenta of the thalassemic mother. Although we have not examined the ferritin level in the cord blood, the mere observation of hemosiderin deposits in the placenta of the thalassemic mother probably reflects iron deposits that could have otherwise been transferred to the fetal circulation.

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Significance of uric acid clearance in preeclampsia

To the Editors:

Although serum uric acid level is useful for estimating the severity of preeclampsia,[1] the level of serum uric acid often overlaps between preeclampsia and normal pregnancy.[2] Decrease in uric acid clearance in preeclampsia has been known,[3] but its use in the precise evaluation of preeclampsia has not been reported. We estimate the usefulness of uric acid clearance in various conditions of pregnancy.

A total of 33 pregnant women (normal pregnancy, 12; preeclampsia, 10; normal pregnancy with chronic glomerulonephritis, 6; superimposed preeclampsia, 5) were studied. Ages of patients ranged from 23 to 39 years. All clinical and laboratory data were obtained from 38 to 40 weeks' gestation and all patients were delivered of infants at 39 to 40 weeks' gestation.

There were no significant differences in serum creatinine levels (normal pregnancy, 0.81 ± 0.02 mg/dl; preeclampsia, 1.00 ± 0.09 mg/dl; normal pregnancy with chronic glomerulonephritis, 1.14 ± 0.09 mg/dl; superimposed preeclampsia, 1.48 ± 0.23 mg/dl; mean ± SEM) or creatinine clearance (normal preg-

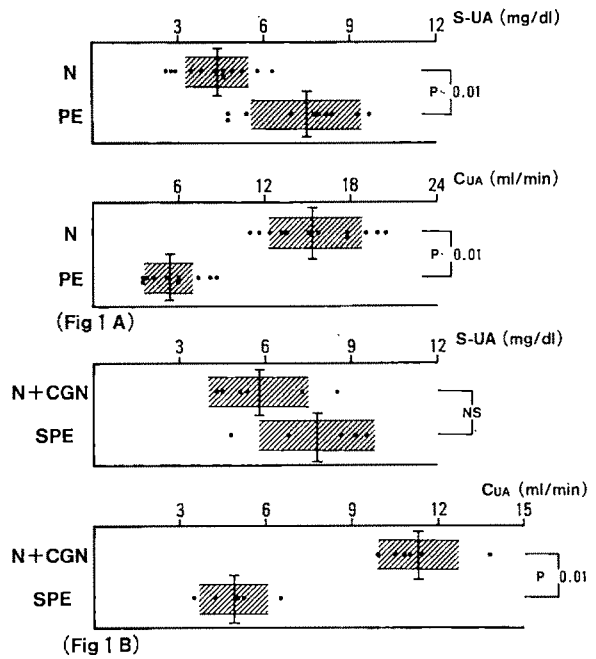


Fig. 1. A, Serum uric acid concentration *(S-UA)* and uric acid clearance *(CUA)* in normal pregnancy *(N)* and preeclampsia *(PE)*. **B,** Serum uric acid concentration *(S-UA)* and uric acid clearance *(CUA)* in normal pregnancy with chronic glomerulonephritis *(N + CGN)* and superimposed preeclampsia *(SPE)*. *Bars* show mean and *shadowed areas* show ±SD.

nancy, 148.7 ± 10.2 ml/min; preeclampsia, 121.4 ± 9.3 ml/min; normal pregnancy with chronic glomerulonephritis, 124.3 ± 14.1 ml/min; superimposed preeclampsia, 95.0 ± 17.2 ml/min). Although the serum uric acid level in preeclampsia (7.5 ± 0.61 mg/dl) increased significantly ($p < 0.01$) compared with that of normal pregnancy (4.4 ± 0.32 mg/dl), this index failed to differentiate preeclampsia from normal pregnancies because of overlap between individual cases in the two groups. On the other hand, these two conditions were clearly distinguished ($p < 0.01$) by uric acid clearance (normal pregnancy, 15.3 ± 0.95 ml/min; preeclampsia, 5.4 ± 0.54 ml/min) that was determined from 24-hour urine collection at the patient's house (Fig. 1, *A*). In pregnant women with chronic glomerulonephritis there was no significant difference in serum uric acid levels between normal pregnancy with chronic glomerulonephritis (5.8 ± 1.70 mg/dl) and superimposed preeclampsia (7.8 ± 0.89 mg/dl). However, uric acid clearance significantly decreased in superimposed preeclampsia (4.9 ± 0.54 ml/min) compared with normal pregnancy with chronic glomerulonephritis (11.3 ± 0.57 ml/min) ($p < 0.01$), and there was no overlap between these two groups (Fig. 1, *B*).

There was significant positive correlation between uric acid clearance and infant birth weight ($r < 0.81$, $p < 0.05$), and negative correlation with mean blood pressure ($r = 0.84, p < 0.01$) in both normal pregnancy and preeclampsia. The birth weight and mean blood pressure during gestation are currently accepted as markers for estimation of the severity of preeclampsia.

In conclusion, although there is no conclusive explanation for a decrease in uric acid clearance in preeclampsia,[4,5] it is one of the most reliable markers for the diagnosis and estimation of the severity of preeclampsia. This index is also useful in the differentiation of superimposed preeclampsia from normal pregnancy with chronic glomerulonephritis.

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Vaginal ultrasonography in the diagnosis of ectopic pregnancy

To the Editors:

We read with interest the article by Dr. Timor-Tritsch et al. (Timor-Tritsch IE, Yeh MN, Peisner DB, Lesser KB, Slavik BA. The use of transvaginal ultrasonography in the diagnosis of ectopic pregnancy. AM J OBSTET GYNECOL 1989;161:157-61) on vaginal ultrasonography in the diagnosis of ectopic pregnancy. It is an excellent addition to the literature on this subject; however, we have a few comments.

The authors state that the visualization of an intrauterine gestation rules out the possibility of an ectopic pregnancy. In 1948 DeVoe[1] initially calculated the incidence of heterotopic pregnancy by multiplying the incidence of fraternal twinning by the incidence of ectopic pregnancy, arriving at the generally quoted figure of 1 in 30,000 pregnancies. Since that time, the incidence of both multiple gestations and ectopic pregnancies has risen (as a result of assisted reproductive technologies, pelvic inflammatory disease, etc.) and the actual incidence of heterotopic pregnancy has been reported to be 1 in 2600 births.[2] Whereas even this number makes the likelihood of finding a heterotopic pregnancy unlikely, if the ultrasonographer does not routinely look for a tubal gestation, even in the presence

of an intrauterine one, there is little chance of making a preoperative diagnosis of an unruptured ectopic pregnancy. This is especially important because the incidences quoted are in a general pregnant population and thus the likelihood of a heterotopic pregnancy is even greater in a symptomatic woman first seen in an emergency room.

The authors noted that all their ruptured ectopic pregnancies had some free pelvic fluid visualized by ultrasonography. Whereas they also state that variable amounts of fluid were noted with unruptured ectopic gestations, the impression left is that fluid noted on ultrasonographic scan is a significant sign of possible tubal rupture. Although fluid in the cul-de-sac should increase the index of suspicion for an ectopic pregnancy, there are two important caveats. First, there are false-positive culdocenteses (ruptured corpus luteum cyst) that clinically mimic an ectopic pregnancy and would also have fluid in the cul-de-sac noted on ultrasonographic examination, thus limiting the specificity of this finding. More importantly, institutions vary in their aggressiveness in attempts to manage an ectopic pregnancy laparoscopically (as evidenced by 45 of 49 patients in this article undergoing laparotomy), and many flow sheets for management of suspected ectopic pregnancies will bypass laparoscopy in favor of laparotomy if there is evidence of tubal rupture. It follows that patients with fluid noted on examination, who otherwise might be candidates for a laparoscopic approach, would be managed with laparotomy if this finding is not put into perspective. Whereas fluid is an important variable and should raise one's index of suspicion for tubal rupture, the literature reports a positive culdocentesis with as many as 65% to 77% of unruptured ectopic pregnancies.[3, 4]

Finally, we wish to congratulate the authors for their excellent clinical study.

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Reply

To the Editors:

We thank Drs. Frishman and Luciano for their comments. They are correct with regard to the possibility of a heterotopic pregnancy and the importance of scanning the adnexa even if an intrauterine pregnancy is evident. This fact has been stressed and restressed in almost all articles on the subject of transvaginal techniques. However, we opted not to deal with this subject although it is a valid observation.

With regard to the presence of fluid in the cul-de-sac in cases of apparently nonruptured or even live tubal gestations, we have the following response.

As inferred by the article, it seems to us that it is very difficult to differentiate a ruptured tube from an unruptured one that is merely leaking blood. We have observed blood leakage in several cases of live and clearly unruptured tubal pregnancies. However, the remarks of Drs. Frishman and Luciano are accurate when they state that the presence of cul-de-sac fluid should arouse the suspicion of a tubal pregnancy. Transvaginal sonography has the ability not only to detect small amounts of fluid but also to image floating particulate matter. This combination in a patient with a clear tubal ring or positive serum β-subunit of human chorionic gonadotropin is indicative of the presence of blood in the pelvis. Consequently, culdocentesis is a superfluous procedure in offices or institutions in which transvaginal sonography is available. It is also more specific and more sensitive than culdocentesis in the diagnosis of pelvic fluid.

From our experience we can make the following observations: (1) the presence of blood in the pelvis is not indicative of the type of ectopic pregnancy; (2) a live tubal ectopic pregnancy may coexist with some blood in the pelvis; (3) a larger amount of pelvic blood is usually indicative of a ruptured ectopic pregnancy or a bleeding tubal abortion; and (4) it seems to be difficult to differentiate between a tubal abortion and a tubal rupture.

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Physician characteristics and cesarean delivery

To the Editors:

The retrospective study by Berkowitz et al. (Berkowitz GS, Fiarman GS, Mojica MA, Bauman J, Haynes de Regt R. Effect of physician characteristics on the cesarean birth rate. AM J OBSTET GYNECOL 1989; 161:146-9) was of interest because of recent personal experiences during the past 2 years at the National Maternity Hospital, Dublin, Ireland. The authors suggest that the observed differences in the cesarean birth rate may be explained by physician characteristics. It is tempting to consider that the trend of a rising cesarean delivery rate is, in part, physician related.

Whereas the validity of rate comparison in different obstetric populations can be questioned, the disturbing

trend of rising cesarean rates has not been observed in Dublin, despite many changes in physician staff.[1,2] In an effort to understand these varying rates the following fundamental concepts must be addressed before "physician characteristics" can be considered: (1) the cesarean sections in nulliparous and multiparous patients must be analyzed separately, (2) primary and repeat cesarean sections should be distinguished, and (3) whether the patient was in labor or not must be recorded. Daily documentation of all cesarean sections, weekly peer review of all cesarean deliveries in nulliparous patients in labor, and monthly review of all cesarean deliveries form an essential prospective audit of obstetric practice in Dublin. Hence the problem of having approximately 10% of cesarean sections without a clear indication does not arise in that institution. The management of labor in the National Maternity Hospital applies to all patients—private and nonprivate. It is these characteristics that are central to the understanding of cesarean birth rates.[3]

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Reply

To the Editors:

Although we agree that such factors as nulliparity, a previous cesarean section, and, to a lesser extent, presence of labor are important determinants of cesarean birth rates, it is unlikely that these factors account for the more than fourfold increase in the rate of cesarean deliveries during the past two decades in the United States. Other contributing reasons also suggested include the improved safety of cesarean procedures for the mother, the increased use of cesarean sections for breech presentations and low-birth-weight fetuses, higher proportions of older primiparous patients, improved third-party reimbursement, and fear of malpractice,[1,2] but some of these factors remain speculative.

Recent studies have also shown that rates of cesarean sections differ between private and clinic patients[3] as well as by socioeconomic status.[4] We also observed that there are large variations in the cesarean section rate among individual physicians caring for private patients at our institution. Thus, we were interested in examining whether these variations could be attributed to such physician characteristics as age, years of experience, gender, and practice setting (solo versus group setting).[5]

It appears reasonable to conclude that there are multiple factors that have led to the dramatic increase in cesarean section rates in the United States. Identification of these factors serves as a first step for establishment of appropriate educational and monitoring programs to safely reduce the current rate of cesarean section.

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Intrauterine growth retardation is not the same as small for gestational age

To the Editors:

I do not agree with Goldenberg et al. (Goldenberg RL, Cutter GR, Hoffman HJ, Foster JM, Nelson KG, Hauth JC. Intrauterine growth retardation: standards for diagnosis. AM J OBSTET GYNECOL 1989;161:271-7) that much of the confusion that presently surrounds intrauterine growth retardation (IUGR) would be eliminated if their recommendations were followed. Indeed, I believe the opposite because they are not discussing a definition of IUGR but rather are defining small-for-gestational-age (SGA) newborns.

Wilcox has mentioned several reasons for not confusing SGA with IUGR.[1] These include:

1. IUGR is probably not confined to the smallest 10% as are SGA newborns
2. SGA infants are a heterogeneous group that includes those who appear normal except for their small size
3. Multiple factors cause a symmetric distribution of term newborn weights. By implication, newborns at extreme weight occur in the absence of pathologic factors and the occurrence of SGA newborns is not preventable
4. IUGR and SGA are two separate concepts

To believe that IUGR is the same as SGA, suggests that at least 10% of fetuses have an unfavorable intrauterine environment. This concept causes a waste of

obstetric resources and patient time, and increases the rate of obstetric interference.

The obstetric signs of an IUGR fetus include indication of relative maternal hypovolemia (hemoconcentration), dysmaturity, oligohydramnios, chronic fetal distress (abnormal biophysical monitoring), and most of all, "a falling off the growth curve."[2] It is hoped that obstetricians will leave the normal SGA fetus alone and will concentrate on treating or rescuing the IUGR fetus.

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Reply

To the Editors:

It appears from his letter that Dr. Goodlin wants, not only us, but all who write in the obstetric literature to use the term small for gestational age (SGA) to describe those babies who weigh less than the tenth percentile birth weight for gestational age and to use intrauterine growth retardation (IUGR) to describe the fetus that is associated with maternal hemoconcentration, dysmaturity, oligohydramnios, and chronic fetal distress. He may wish it, but most authors who write in the obstetric literature today do not agree, and define IUGR as less than the tenth percentile birth weight for gestational age. Therefore, in our use of the term *IUGR* we adhered to the common usage. Most important, in this article we very carefully defined the condition under discussion as birth weight for gestational age less than the tenth percentile.

We do happen to agree with Dr. Goodlin that all babies who weigh less than the tenth percentile for gestational age, whether they are called IUGR or SGA, are a heterogenous group that often includes some infants who appear normal except for their small size. We also would agree with him that there are infants outside the tenth percentile who apparently have the genetic potential to be larger, but because of environmental or other factors do not reach their full growth potential. We also would agree with Dr. Goodlin that "It is hoped that obstetricians will leave the normal SGA fetuses alone and will concentrate on treating or rescuing the IUGR fetus."

Nevertheless, whereas it would be very nice to know each infant's ultimate potential for growth and then to compare this potential to the growth actually attained, deriving such data is problematic at best. However, as a first step we thought it would be important for a uniform standard to define the tenth percentile to be used from study to study. We stand by our suggestion that the development of a concensus on the birth weight used to define the tenth percentile birth weight at each gestational age would *decrease,* not increase confusion. Until one can agree on a practical definition of the "extremes" of birth weight, there is not even a starting point to discuss with other investigators the proportion of those infants "at extreme weight" who may be normal or abnormal, or to define the risk factors for and the ultimate outcomes associated with reduced fetal growth.

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Calculation of ritodrine half-life

To the Editors:

I read with interest the informative report of Dr. Caritis et al. (Caritis SN, Venkataramanan R, Cotroneo M, Chiao J-P. Pharmacokinetics of orally administered ritodrine. AM J OBSTET GYNECOL 1989; 161:32-5) and agree with the authors that the plasma concentrations of ritodrine suggest that the maximal dose for oral administration should be increased. However, I am interested in the methods used in the calculation of the half-life (Table II). The authors present a half-life of ritodrine of 166 minutes in fed patients. However, the peak level of 8.3 ng/ml at 78 minutes and level of 1.7 ng/ml at 240 minutes would suggest a greater than fourfold decrease in 162 minutes. A similar study of oral ritodrine pharmacokinetics[1] indicated an initial half-life of 1.2 hours and a second phase half-life of 14 hours.

There are many difficulties in determining half-life after a single oral administration, including the precise detection of the time of peak drug concentration, the continued absorption of the drug throughout the decay period, and the appropriate modeling of the clearance pathways.[2] Would the authors please provide additional information with regard to their methods of calculation?

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2. DiStefano JJ III. Concepts, properties, measurement, and computation of clearance rates of hormones and other substances in biological systems. Ann Biomed Eng 1976;4: 302-19.

Reply

To the Editors:

Dr. Ross raises two questions. First, he questions why the decrease in ritodrine concentration from the peak value appears to be more rapid than expected if the half-life of the drug was 166 minutes. He also asks how we calculated the half-life because our value differs from what has been previously published.[1]

After ritodrine is absorbed, it is distributed to extravascular sites. Plasma concentrations decrease rapidly during this distribution phase. After distribution is complete, plasma concentrations decrease slowly. This disposition phase reflects ritodrine metabolism or excretion.[2] The clinically pertinent half-life is the one obtained during the disposition phase. In this study, we used noncompartmental methods to calculate the disposition phase half-life. The terminal slope of the plasma concentration versus time curve was calculated by linear regression analysis of the log concentration versus time data. We used at least three data points to calculate the disposition half-life. Thus, in response to Dr. Ross' first question, the ritodrine concentration falls rapidly between 78 to 120 minutes because of drug distribution. The mean disposition half-life of 166 minutes is calculated after distribution is complete.

The article referenced by Dr. Ross reports a single case in which ritodrine concentration was measured after oral administration to a nonpregnant subject.[1] The cited study used radioimmunoassay to measure ritodrine and the terminal disposition half-life was determined on several plasma concentration values that were <1 ng/ml. The radioimmunoassay is unlikely to be sufficiently sensitive or specific for ritodrine to accurately measure plasma concentrations <1 ng/ml. Thus these estimates of half-life are unlikely to be correct. Further, we have shown marked differences in ritodrine kinetics between pregnant and nonpregnant human beings.[2,3] The disposition half-life in pregnancy averages 156 minutes whereas, in nonpregnant volunteers it averages 366 minutes. Finally, our calculated disposition half-life of 166 minutes is very similar to that previously determined for ritodrine after intravenous infusion.[2]

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BOARD CERTIFICATION

The American Board of Obstetrics and Gynecology, Inc.

New certifications: Subspecialty of Basic

Date of examination: December 1989

Place: Chicago, Illinois

Number certified this examination: 1035*

Certification for these individuals is time-limited, and the period of certification is December 8, 1989, through December 31, 1999.

Cumulative total certificates awarded for this subspecialty: 28,818

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del Valle, Rene C., 201 Hickory Blvd., McMinnville, TN 37110

New certifications: Subspecialty of Reproductive Endocrinology

Date of examination: December 1989

Place: Chicago, Illinois

Number certified this examination: 36

Cumulative total of certificates awarded for this subspecialty: 370

Awadalla, Sherif G., Bethesda Fertility Ctr., 619 Oak St., 3 South, Cincinnati, OH 45206
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Cassels, John Wesley, Jr., 7412 97th Ave., S.W., Tacoma, WA 98498
Cedars, Marcelle Ivonne, 231 Bethesda, Ave., ML 526, Cincinnati, OH 45267
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New certifications: Subspecialty of Maternal-Fetal Medicine

Date of examination: December 1989

Place: Chicago, Illinois

Number certified this examination: 42

Cumulative total of certificates awarded for this subspecialty: 560

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New certifications: Subspecialty of Gynecologic Oncology

Date of examination: December 1989

Place: Chicago, Illinois

Number certified this examination: 20

Cumulative total of certificates awarded for this subspecialty: 374

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Recertifications: Subspecialty of Basic

Number recertified this examination: 283

Recertifications effective as of December 8, 1989

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Assessment & Care of the Fetus. Edited by Robert D. Eden and Frank H. Boehm. 1013 pages, illustrated. East Norwalk, Connecticut, 1989, Appleton & Lange. $98.00.

Basic and Advanced Colposcopy: A Practical Handbook for Diagnosis and Treatment. Edited by V. Cecil Wright and Gordon M. Lickrish. 266 pages, illustrated. Houston, 1989, Biomedical Communications, Incorporated. $38.00.

Biologic Markers in Reproductive Toxicology. Donald R. Mattison, et al. 359 pages, illustrated. Washington, D.C., 1989, National Academy Press. $27.95.

Breast Disease for Gynecologists. William H. Hindle. 288 pages. East Norwalk, Connecticut, 1989, Appleton & Lange. $73.00.

Chemotherapy of Gynecological and Breast Cancer. M. Kaufmann, F. Kubli, P. Drings, H. Burkert, and G. Bastert. 94 pages, illustrated. Switzerland, 1989. $21.50.

Clinical Cytopathology and Aspiration Biopsy. Ibrahim Ramzy. 411 pages, illustrated. East Norwalk, Connecticut, 1989, Appleton-Century-Crofts. $90.00.

Conception to Birth. Edited by Jennie Kline, Zena Stein, and Mervyn Susser. 433 pages, illustrated. New York, 1989, Oxford University Press. $55.00.

The Couple's Guide to Fertility. Gary S. Berger, Marc Goldstein, and Mark Fuerst. 442 pages, illustrated. New York, 1989, Doubleday. Hard cover $22.95, paperback $12.95.

Danforth's Obstetrics and Gynecology. Edited by James Scott and Charles Hammond. 1328 pages, illustrated. Philadelphia, 1989, J.B. Lippincott Company. $89.50.

Drug Use in Pregnancy: Mother and Child. Edited by Ira J. Chasnoff. 163 pages, illustrated. The Netherlands, 1989, Kluwer Academic Publisher Group. U.S. $48.00, U.K. $31.75.

Fetal and Neonatal Physiological Measurements. III. Edited by Gerhard Gennser, Karel Marsal, Nils Svenningsen, and Kjell Lindstrom. 547 pages, illustrated. Sweden, 1989. The Third International Conference on Fetal and Neonatal Physiological Measurements. No price listed.

Guide to Clinical Preventive Services. Edited by Michael Fisher. 419 pages. Baltimore, 1989, Williams & Wilkins. $19.95.

Handbook of Contraception and Abortion. Ronald T. Burkman. 152 pages, illustrated. Boston, 1989, Little, Brown & Company. $19.50.

How It Feels to Fight for Your Life. Jill Krementz. 132 pages, illustrated. Boston, 1989, Little, Brown & Company. U.S. $15.95, Canada $19.95.

Manual of Gynecologic Oncology and Gynecology. Edited by M. Steven Piver. 401 pages, illustrated. Boston, 1989, Little, Brown & Company. $22.50.

Obstetrics & Gynecology Annual Review. Harrison Sheld. 321 pages. Oxford, 1989, Pergamon Press. $32.51.

Operative Gynecologic Endoscopy. Edited by J. S. Sanfilippo and R. L. Levine. 325 pages, illustrated. New York, 1989, Springer-Verlag. No price listed.

Premenstrual, Postpartum, and Menopausal Mood Disorders. Laurence Demers, John McGuire, Audrey Phillips, and David Rubinow. 224 pages, illustrated. Baltimore, 1989, Urban & Schwarzenberg. $36.50.

Prenatal Diagnosis in Obstetrics. Edited by M. J. Whittle and J. M. Connor. 274 pages, illustrated. London, 1989, Blackwell Scientific Publications. No price listed.

Radiographic Measurements. Edited by Robert Rosenberg, 125 pages, illustrated. Philadelphia, 1989, J. B. Lippincott Company. $14.95.

Relaxing with Yoga During Pregnancy. Leslie Goldstein. Cassette tape, illustrated booklet. Cambridge, 1989, Rudra Press. $11.95.

Sexuality: An Illustrated History. Edited by Sander L. Gilman. 367 pages, illustrated. New York, 1989, John Wiley & Sons. No price listed.

Sixteenth Annual Report of Cancer Research: The University of Chicago. Edited by Lisa Claxton Moore, 393 pages. Chicago, 1989. No price listed.

Staying Dry: A Practical Guide to Bladder Control. Kathryn Burgio, K. Lynette Pearce, and Angelo Lucco. 169 pages, illustrated. Baltimore, 1989, The John Hopkins University Press. Hard cover $24.00, soft cover $12.95.

Safety Requirements for Contraceptive Steroids. Edited by F. Michal. 467 pages, illustrated. New York, 1989, Cambridge University Press. $110.00.

The Testis. Second edition. Edited by Henry Burger and David DeKretser. 605 pages, illustrated. New York, 1989, Raven Press. $110.00.

ITEMS

Announcements of major meetings and other significant activities must be received at least 8 weeks before the desired month of publication. All announcements carry a charge of $60.00 U.S. per insertion and the fee must accompany the request to publish. Information will be limited to title of meeting, date, place, and an address to obtain further information. Send announcements and payment, payable to this JOURNAL, to Kay G. Goehler, Senior Manuscript Editor, Journal Editing, Mosby-Year Book, Inc., 11830 Westline Industrial Drive, St. Louis, Missouri 63146-3318.

Perinatal Dilemmas, a national conference of interest to both physicians and nurses in the fields of obstetrics and neonatology, August 6-10, 1990, at the Snow King Resort, Jackson Hole, Wyoming. ACOG and ANA approved for 19 credit hours. For complete brochure contact: Contemporary Forums: 530 La Gonda Way, Suite E, Danville, CA 94526. Tel.: (415) 820-2800, ext. 157.

Recent Advances in Obstetrics and Gynecology, Omni Netherland Plaza Hotel, Cincinnati, Ohio, October 4-6, 1990. Sponsored by the Departments of Obstetrics and Gynecology, University of Cincinnati College of Medicine, Good Samaritan Hospital, and The Christ Hospital. For information, contact Course Coordinator, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, 231 Bethesda Ave., Cincinnati, OH 45267-0525. Tel.: (513) 558-8440.

High Risk/Critical Care Obstetrics: Medical & Nursing Management of the 90's, Hamilton Princess Resort, Bermuda, August 11-18, 1990. For conference information contact: Jim Goodrich, CMP, Symposia Medicus, 2815 Mitchell Dr., Suite 128, Walnut Creek, CA 94598-1622. Tel.: (415) 935-7889.

NCHS to hold data users conference in August 1990. Users of data files from the National Center for Health Statistics will have a special opportunity to expand their knowledge of data resources when the National Center for Health Statistics holds its fifth biennial Data Users Conference, August 15-17, 1990, in Rockville, Maryland. The conference provides users the forum to learn of current and potential applications for the public use data sets, discuss technical and analytical issues with NCHS staff, and exchange information with other data users. A plenary session will provide a preview of future directions in data collection, analysis, and dissemination by NCHS. NCHS Director Dr. Manning Feinleib will deliver the keynote address. The 3-day conference program consists of 38 workshops on specific data files from the many NCHS data systems, as well as sessions on cross-cutting topical and analytical issues. Special sessions will be devoted to NCHS data on: health of minorities, occupational and environmental health, health and health care needs of an aging America, and HIV infection and AIDS. In addition, there will be presentations on the Center's cognitive research program to improve the quality and collection of national health statistics, on software developments, on the integrated survey design for NCHS data systems, and on new technologies in cartography and graphics. First-time conference attendees can take advantage of an overview of NCHS data systems, intended for those who are looking for more guidance about the types of data gathered by NCHS, before attending the in-depth workshops. NCHS is the federal government's primary vital and health statistics agency and is a part of the Centers for Disease Control, Public Health Service. Through interview, health examination, and health record surveys and the vital statistics system, NCHS produces a wide array of health and health-related data. More than 600 public use data files are available representing data from the more than a dozen separate data systems. There is no registration fee for the conference, but space is limited. To receive an invitation and registration packet, contact: Barbara Hetzler, NCHS, Room 1100, 6525 Belcrest Road, Hyattsville, MD. Tel.: (301) 436-7122.

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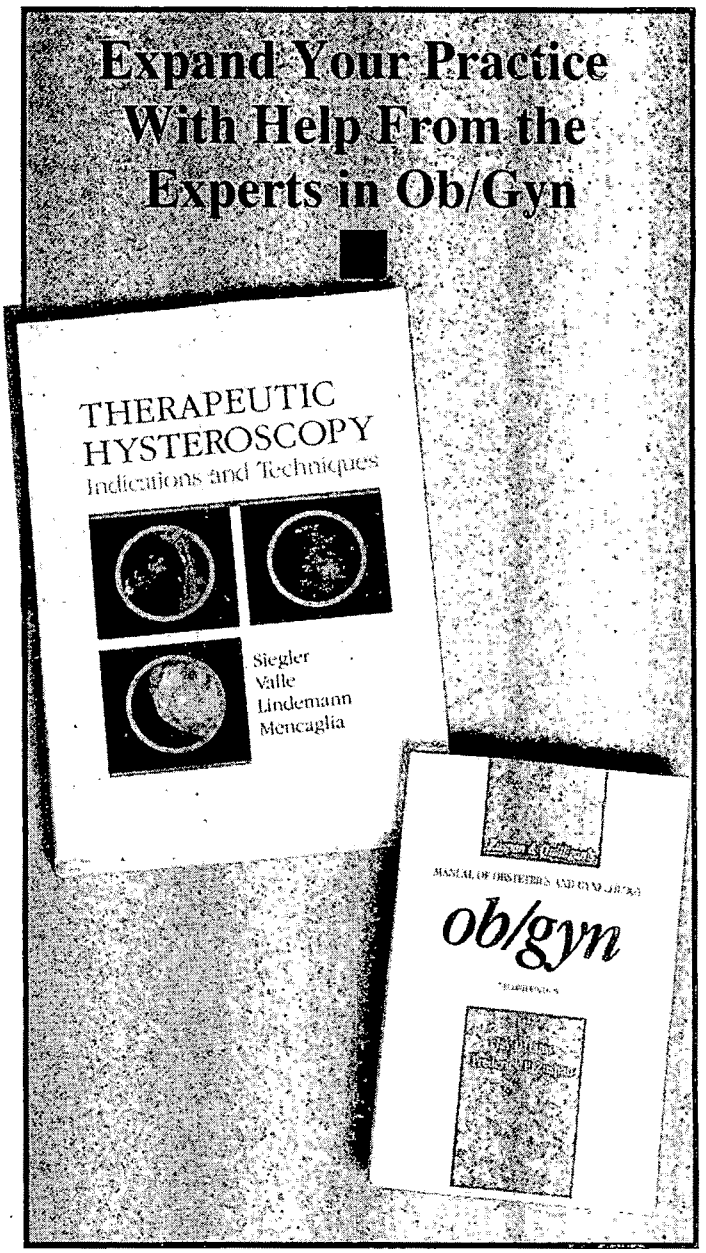
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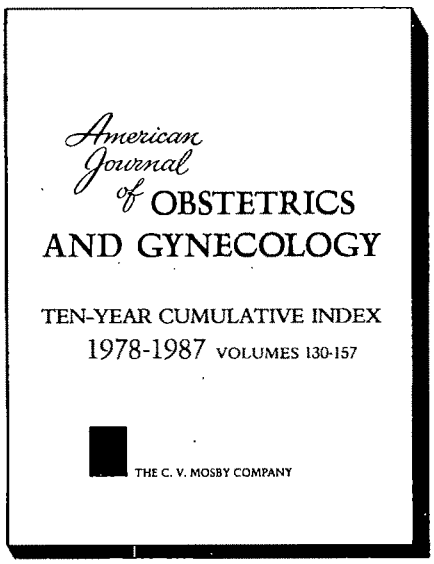
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ATTENDING PHYSICIANS OBSTETRICS & GYNECOLOGY

Kings County Hospital Center, one of the nation's largest university affiliated medical centers, is seeking Attending Physicians for Obstetrics and Gynecology. Responsibilities include resident and student education, supervision of resident physicians, and direct patient care.

A highly competitive starting salary and benefits package are offered. Excellent opportunities for research. Academic appointment at SUNY, Health Science Center at Brooklyn, is available, depending on qualifications.

Candidates must have completed an ACGME approved training program, be Board Certified or Eligible, and possess a New York State license.

Interested applicants should send letters with curriculum vitae and salary history to: Lillie K. Marwieh, Assistant Personnel Director.

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Obstetrics/ Gynecology

WISCONSIN: Marshfield Clinic, a multi-specialty group practice with 350 physicians is seeking BE/BC obstetricians/gynecologists to join expanding (40-50 physician) regional centers in Chippewa Falls and Woodruff, Wisconsin. A third OB/GYN is needed for each facility. Chippewa Falls is located 1 1/2 hours from downtown Minneapolis/St. Paul and twenty minutes from a major four year campus of the University of Wisconsin. Known as the "Lakeland Area" (over 1,000 navigable lakes) Woodruff is truly one of the most attractive vacation areas in the upper Midwest and renown for its year-round outdoor recreational activities. Both communities offer exceptional recreational, cultural, and educational opportunities. An emphasis on quality practice and life-style is combined with a total compensation package on reaching membership in excess of $200,000. Starting salary negotiable. Fringe benefit package outstanding; includes self-insured malpractice. No start-up expense. Send C.V. and references to:

David L. Draves
Director, Regional Development

1000 North Oak Avenue
Marshfield, Wisconsin 54449
or call collect at
(715)387-5376

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For a physician application, please call (800) 328-5278. If calling from outside of California, please (800) 541-7946 or send curriculum vitae to: Irwin P. Goldstein, M.D., Associate Medical Director, SCPMG, Dept. 006, Walnut Center, Pasadena, CA 91188-8013. Equal Opportunity Employer M/F/H

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For information contact: Brent Burgee, M.D., Hitchcock Associates of Randolph/ Ob-Gyn, 1 Maple Street, Randolph, Vermont 05060; (802) 728-4431.

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Send CV To: Joyce Leslie, M.D., Planned Parenthood of Tompkins County, 314 W. State St., Ithaca, NY 14850.

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St. Joseph's Hospital & Medical Center in Phoenix, Arizona, a licensed 626-bed, full-service teaching facility and tertiary care center, is seeking an OB/GYN Generalist.

This is an exceptional opportunity in a rapidly growing area of the beautiful Southwest.

Please direct inquiries and curriculum vitae to:

James R. Mouer, M.D.
Associate Director, PIROG
St. Joseph's Hospital & Medical Center
222 W. Thomas Rd., Suite 213
Phoenix, Arizona 85013
(602) 285-3715

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OB/GYN BC/BE two positions available in Oklahoma for hospital based practice. New, fully equipped, LDRP facility, with central fetal monitoring, telemetry, dedicated staff and 24 hour obstetrical anesthesia and family prenatal classes. Level I and II nurseries, strong Pediatrician support. Progressive community with college, symphony and cultural opportunities. Malpractice rates reasonable. Salary and benefits guaranteed. Reply with CV to Medical Staff Office, Room 3122, P.O. Box 205, Oklahoma City, Oklahoma 73101.

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St. Luke's Hospital is actively recruiting board certified/board eligible OB/GYNs for the newly established maternity department. An excellent salary, malpractice insurance, health insurance and moving expenses are among the many benefits that this opportunity offers.

St. Luke's Healthcare Association, a 414-bed multi-facility system, anticipates opening the new 10-bed LDRP unit in early 1991. Saginaw is located 100 miles northwest of Detroit and 15 miles south of the Saginaw Bay near Michigan's "Thumb."

For more information, in confidence, respond with curriculum vitae or call: Debra Hartman, Bronson Management Services Corporation, 210 East Vine Street, Kalamazoo, Michigan 49001 (800) 594-9022.

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C.V. to Seymour Herschberg, M.D.
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NORTHERN CALIFORNIA

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• SAN JOSE •

We are currently seeking a Reproductive Endocrinologist to establish and run a reproductive endocrinology subdivision in the department. Duties would include the full spectrum of reproductive endocrinology, outpatient and surgical management of infertility. Fellowship certification would be preferred. The department currently has 17 physicians and is still growing. We offer a generous benefits package including full coverage malpractice insurance. San Jose has beautiful weather and excellent access to Bay Area recreational and cultural activities.

For more information, please contact: Jerome L. Nehemiah, M.D., Chief, Department of OB/GYN, The Permanente Medical Group, Inc., 260 International Circle, Dept. AJOBG, San Jose, CA 95119, or call collect (408) 972-6180. EOE

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CHAIRPERSON, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, MEHARRY MEDICAL COLLEGE

The School of Medicine of Meharry Medical College invites applications from and nominations of candidates for the position of Professor and Chairman of its Department of Obstetrics and Gynecology. Affiliated institutions include Metropolitan General Hospital in Nashville, TN, and Blanchard Army Hospital in Ft. Campbell, KY. Chair responsibilities include the continuing development of the Department, direct patient care, teaching and research. The candidate must be board certified, have a record of scholarly contributions to the literature and participation in professional organizations and possess strong leadership qualities. An administrative background would be desirable. Nominations or applications should include a curriculum vitae and three references. Please forward no later than July 1, 19890 to:

Harold D. Thompson, M.D.
Chairman, Search Committee for
Obstetrics and Gynecology
Meharry Medical College
1005 D.B. Todd Blvd.
Nashville, Tennessee 37208

UCLA INTERCAMPUS MEDICAL GENETICS TRAINING PROGRAM

The UCLA intercampus post-doctoral research training program in Medical Genetics utilizes the research and clinical resources of its affiliated campuses an teaching hospitals. The program is open to academically oriented applicants with the M.D., Ph.D., D.D.S. or equivalent degrees. A wide variety of research training opportunities in molecular, biochemical, immuno-, cancer, cyto-, somatic cell, population and clinical genetics are available. The program also meets all the requirements of the American Board of Medical Genetics. Clinical genetics fellowships are available at each of the affiliated hospitals. Application forms are available from David Minoin, M.D., Ph.D., Department of Pediatrics, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048.

Postdoctoral Training Program in Medical Genetics

The Interdepartmental Medical Genetics Program at Stanford University School of Medicine provides advanced clinical and/or research training related to human inherited disease. Well-represented areas of the program include:

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Individuals with an MD, PhD, or equivalent degree are eligible for this three-year program which includes an extended period of research training with one of twenty-six training faculty and the opportunity to pursue applied training in clinical genetics, clinical cytogenetics, or molecular genetics in an ABMG-accredited setting. Minority individuals are especially encouraged to apply. For information and application forms, contact:

Uta Francke, M.D.
Departments of Genetics and Pediatrics
Howard Hughes Medical Institute
Stanford, California 94305-5428

FACULTY POSITIONS CALIFORNIA

LOS ANGELES COUNTY/ OLIVE VIEW MEDICAL CENTER

DIRECTOR OF MATERNAL- FETAL MEDICINE: Beautiful new state-of-the-art UCLA affiliated teaching hospital seeks director of a three-member division. Candidate should be a senior, experienced leader, board certified in maternal-fetal medicine, with investigative abilities. The position includes faculty appointment at UCLA School of Medicine.

GENERAL OBSTETRICIAN/GYNECOLOGIST: Board eligible/certified Obstetrician/Gynecologist to join twelve full-time hospital based academic physicians. Assignments include obstetrics, gynecology and outpatient services with emphasis on resident teaching/supervision. Clinical research encouraged. The position requires a faculty appointment at UCLA School of Medicine.

Olive View Medical Center is a 377-bed acute care facility located in the San Fernando Valley 25 miles north of the UCLA campus in Westwood. It serves a catchment population in excess of two million. It is an integral part of the UCLA student and residency training program in obstetrics and gynecology. Twelve obstetric and gynecology residents are assigned to Olive View. Over 7,000 high risk obstetrical patients are delivered yearly supported by a fully staffed antenatal testing unit, obstetrical anesthesia and neonatalogy/NICU coverage as well as full internal medicine, surgery, pediatrics and emergency medicine services.

Please apply with curriculum vitae to:
George Mikhail, M.D., Chairman
Department of Obstetrics and Gynecology
OLIVE VIEW MEDICAL CENTER
14445 Olive View Drive
Sylmar, CA 91342-1495

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OB/GYN WISCONSIN

Multi-specialty group in suburban Milwaukee seeks BC/BE Obstetrician/Gynecologist to join 6 physician OB/GYN department. Single site, single hospital practice. Competitive salary and fringe benefits. Forward inquiries and CV to:

Administrator
P.O. Box 427
Menomonee Falls, WI
53051

Incredible Obstetrics/Gynecology opportunity 1½ hours north of Tulsa in beautiful Eastern Kansas. $250,000 net income plus signing bonus. Sponsored by stable and wealthy hospital system. Total medical staff support. Brand-new $1.5 million single room maternity addition and offices. Contact Dirk Smith, Jackson and Coker, 115 Perimeter Center Place, Suite 380 AJOG0, Atlanta, GA 30346, Tel. 1-800-544-1987.



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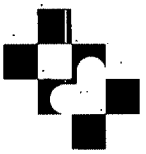
Fairview, a community hospital in the Berkshire Hills of western Massachusetts, is seeking a Board Certified or eligible OB/GYN to join as associate in an established practice; also, to direct active Prenatal Center.

Our hospital serves several communities (approximate population 30,000) in an ideal rural environment with an abundance of cultural activities, excellent school systems, and proximity to both New York and Boston.

We offer a two-year practice guarantee as part of a generous benefits package.

Please forward C.V.s to Mary J. Washburn, Recruitment Coordinator, Fairview Hospital, 29 Lewis Avenue, Great Barrington, Massachusetts 01230. Our telephone number is 1-413-528-0790.

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Fargo Clinic
MeritCare

OB-GYN

Large multispecialty group is seeking BC/BE Obstetrician-Gynecologist to join seven member department. Department is active in donor and husband insemination. Opportunity to develop Invitro and Gift Programs available.

Fargo Clinic is a 250 physician group that practices in 30 locations throughout eastern ND and western MN. The main facility is located next to St. Luke's Hospitals, a 400 bed tertiary care & trauma center. St. Luke's is a NACHRI designated Children's Hospital with a level III ICN.

Fargo-Moorhead is a tri-college community of 130,000 located just minutes from the lake country of western Minnesota. Abundant cultural, recreational, sporting and hunting activities available year around.

Outstanding compensatory package available. Respond to Robert C. Montgomery, M.D., Chairman, Physician Recruitment, 737 Broadway, Fargo, ND 58123.

BLUE RIDGE MOUNTAINS VIRGINIA

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OBSTETRICS/ GYNECOLOGY

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Bemidji Clinic is affiliated with a 250 physician multispecialty group located in Fargo, ND and affiliated with a 400 bed level II hospital with a 24 level III Intensive Care Nursery.

Excellent compensation and benefit package with incentive pay plan. To discuss this exceptional opportunity further please contact C. C. Lowery, Administrator, Bemidji Clinic, 1233 34th St. NW, Bemidji, MN 56601 or call 1-218-751-1280.

BRIGHAM AND WOMEN'S HOSPITAL

Perinatologist

The Brigham and Women's Hospital, a major teaching hospital of Harvard Medical School, seeks a full-time perinatologist to join the Division of Maternal-Fetal Medicine.

Applicants should be Board-certified or active candidates for certification in Obstetrics and Gynecology and Maternal-Fetal Medicine.

Academic rank will be commensurate with experience and achievements.

Commitment to clinical care, research, and teaching are essential.

Send inquiry and curriculum vitae to:

Michael F. Greene, M.D.
Director, Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Brigham and Women's Hospital
75 Francis Street, ASB1-3-078
Boston, MA 02115

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The course will be directed by **Professor Geoffrey Chamberlain** and **Mr Malcolm Pearce** of the Department of Obstetrics and Gynaecology, St George's Hospital Medical School, University of London.

The course is aimed at consultants and specialists in obstetrics and gynaecology. It is essentially a clinical course with a scientific background; most of the speakers are in charge of the clinical practice of modern obstetric care, but have performed basic research in their own clinical area.

There are vacancies for 30 participants.

Course fee: £805; accommodation charge: £535; total fee: £1340.

The working sessions will be held at St George's Hospital Medical School. Resident participants will be accommodated at a hotel in rooms with private bath or shower.

The British Council

Further information and application forms are available from British Council Representatives overseas or from Courses Department, The British Council, 65 Davies Street, London W1Y 2AA.

OBSTETRICS & GYNECOLOGY

Obstetrician/Gynecologist needed to join a five physician department at a major regional multispecialty clinic in Billings, Montana. Clinic setting includes all specialties and is adjacent to an outstanding tertiary care referral hospital. Excellent opportunity for a top notch board eligible or board certified Obstetrician/Gynecologist looking for a challenging practice in a geographic area offering unlimited recreational potential. Those interested send CV to:

John W. Heizer, M.D.,
Medical Director
The Billings Clinic
P.O. Box 35100
Billings, Montana 59107-5100

BRIGHAM AND WOMEN'S HOSPITAL

Obstetrician/Gynecologist

The Brigham and Women's Hospital, a major teaching hospital of Harvard Medical School, seeks several obstetrician/gynecologists to join a busy full-time faculty group practice in general obstetrics and gynecology. The practice is located in a private setting near the hospital.

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Offers competitive economic package and generous fringe benefits.

Commitment to clinical care and teaching are essential.

Send inquiry and curriculum vitae to:

Kenneth J. Ryan, M.D.
Chairman
Department of Obstetrics and Gynecology
Brigham and Women's Hospital
75 Francis Street, ASB1-3-073
Boston, MA 02115

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OBSTETRICS/GYNECOLOGY

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Wahpeton/Breckenridge has a combined population of 15,000 with a patient draw area of over 40,000. Wahpeton is the home of the ND State College of Science and each community has public and parochial primary education.

Will join a 250 physician multispecialty group affiliated with a 400 bed level II hospital which has a NACHRI designated Children's Hospital and a 24 bed level III ICN.

For further information regarding this excellent practice opportunity please contact Robert Ostmo, M.D., 227 6th St. N., Breckenridge, MN 56520 or call 1-218-643-7813.

FACULTY POSITION
DIVISION OF MATERNAL-FETAL MEDICINE
ALBANY MEDICAL COLLEGE

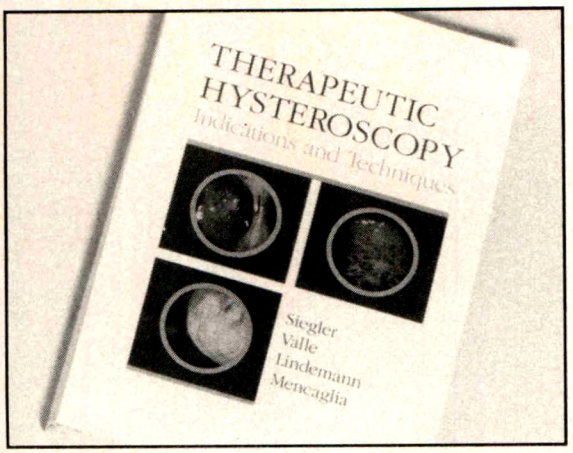
Rapidly expanding division in our Department of Ob/Gyn needs a board eligible/certified individual. Candidates should have a strong background in obstetric ultrasound as well as a commitment for medical student and resident education. Protected time for research and other academic pursuits guaranteed. New facility nearing completion. Academic rank in accordance with experience. Competitive salary plus attractive faculty incentive plan provided.

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INTERESTED CANDIDATES SHOULD SEND A LETTER OF INTEREST WITH CV TO:

Myron Gordon, M.D.
Chairman, Department of OB/GYN
Albany Medical College A-74
47 New Scotland Avenue
Albany, New York 12208
OR
Paul J. Weinbaum, M.D.
Head, Division of Maternal-Fetal Medicine
Department of OB/GYN A-133

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Elko Regional Medical Center
762-14th Street
Elko, Nevada 89801
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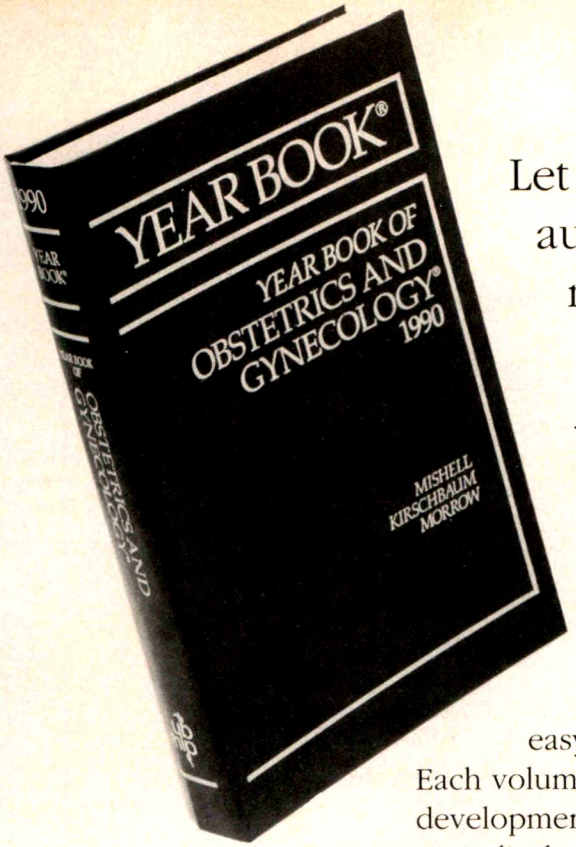
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INDICATIONS AND USAGE: PREVENTION OF PREGNANCY.

CONTRAINDICATIONS: Oral contraceptives should not be used in women who currently have the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophlebitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected carcinoma of the breast. 5. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Cholestatic jaundice of pregnancy or jaundice with prior pill use. 8. Hepatic adenomas or carcinomas. 9. Known or suspected pregnancy.

WARNINGS

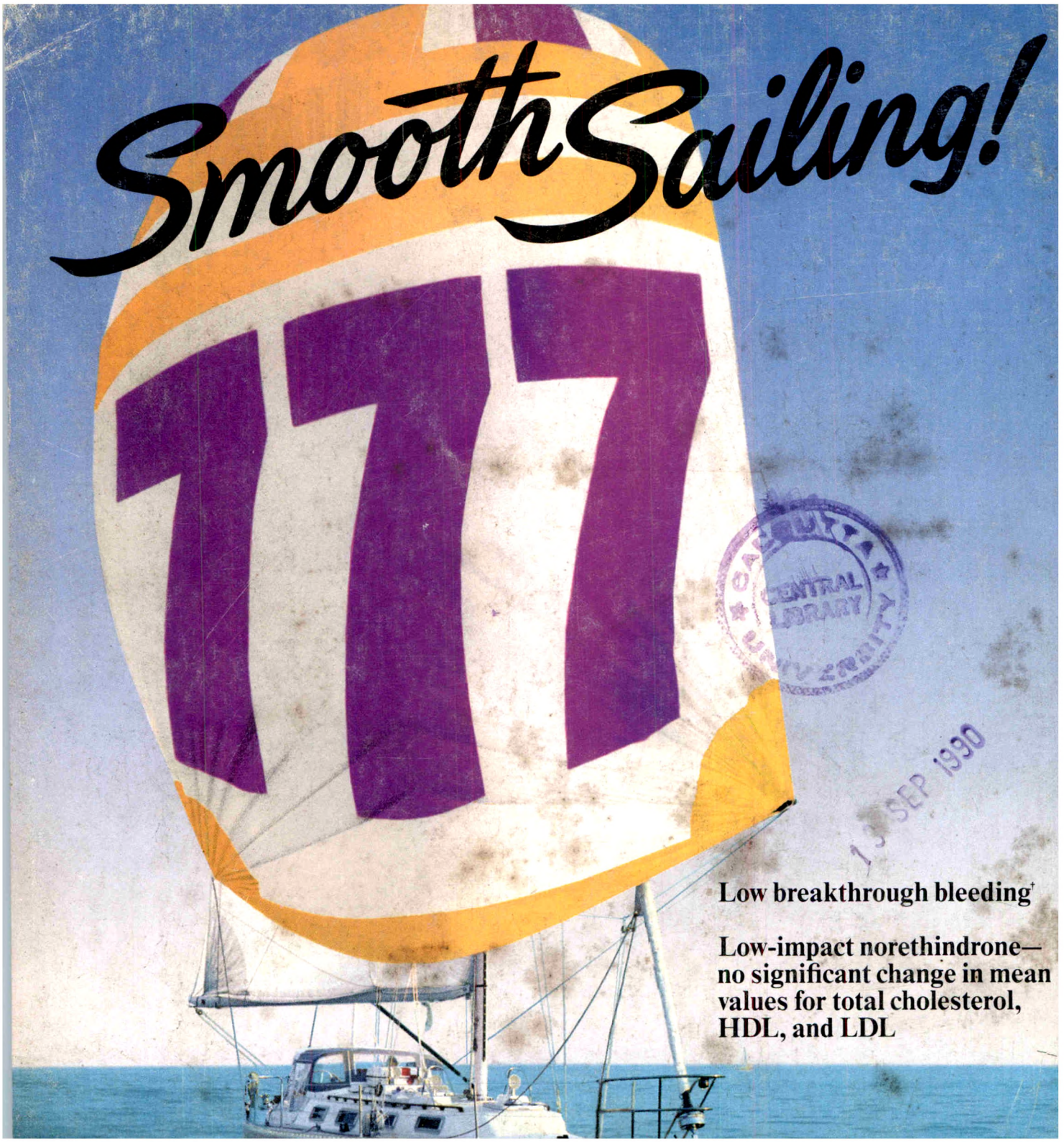
Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this brief summary is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined. Throughout this brief summary epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods. 1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. a. Myocardial Infarction. An increased risk of myocardial infarction has been associated with oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives. Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors. b. Thromboembolism. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed. c. Cerebrovascular diseases. Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users, for both types of strokes, and smoking interacted to increase the risk of stroke. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. d. Dose-related risk of vascular disease from oral contraceptives. A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptive. The activity and amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen. e. Persistence of risk of vascular disease. There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens. 2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE. One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. However, smokers 35 and older and non-smokers 40 and older who use oral contraceptives have a significant increase in mortality higher than those using other methods of birth control. These facts must be weighed in conjunction with failure rates for other methods and the risk associated with subsequent pregnancy. 3. CARCINOMA OF THE REPRODUCTIVE ORGANS. Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. While there are conflicting reports most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. 4. HEPATIC NEOPLASIA. Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. 5. OCULAR LESIONS. There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately. 6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY. Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out. 7. GALLBLADDER DISEASE. Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens. 8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users. This effect has been shown to be directly related to estrogen dose. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives. A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users. 9. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with extended duration of use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity. Women with a history of hypertension or hypertension-related diseases, or renal disease, should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users. 10. HEADACHE. The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause. 11. BLEEDING IRREGULARITIES. Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent. 12. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. **PRECAUTIONS:** 1. PHYSICAL EXAMINATION AND FOLLOW UP. A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. 2. LIPID DISORDERS. Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. 3. LIVER FUNCTION. If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function. 4. FLUID RETENTION. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. 5. EMOTIONAL DISORDERS. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 6. CONTACT LENSES. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. 7. DRUG INTERACTIONS. Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines. 8. INTERACTIONS WITH LABORATORY TESTS. Certain endocrine and liver function tests and blood components may be affected by oral contraceptives: a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability. b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radio-immunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. c. Other binding proteins may be elevated in serum. d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged. e. Triglycerides may be increased. f. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives. 9. CARCINOGENESIS. See WARNINGS section. 10. PREGNANCY. Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections. 11. NURSING MOTHERS. Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child. **INFORMATION FOR THE PATIENT: See Patient Package Insert. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section). Thrombophlebitis and venous thrombosis with or without embolism. Arterial thromboembolism. Pulmonary embolism. Myocardial infarction. Cerebral hemorrhage. Cerebral thrombosis. Hypertension. Gallbladder disease. Hepatic adenomas or benign liver tumors. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea. Vomiting. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Amenorrhea. Temporary infertility after discontinuation of treatment. Edema. Melasma which may persist. Breast changes: tenderness, enlargement, secretion. Change in weight (increase or decrease). Change in cervical erosion and secretion. Diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome. Cataracts. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. Hemolytic uremic syndrome. Acne. Changes in libido. Colitis. **OVERDOSAGE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

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NORINYL® 1 + 35 21-Day Tablets (norethindrone 1 mg with ethinyl estradiol 0.035 mg)
NORINYL® 1 + 35 28-Day Tablets (21 norethindrone 1 mg with ethinyl estradiol 0.035 mg tablets followed by 7 inert tablets)
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NOR-Q.D.® (norethindrone) Tablets 0.35 mg
ORAL CONTRACEPTIVE (O.C.) AGENTS

Indications: Prevention of pregnancy.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who have the following conditions:
- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium, and known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas, carcinomas or benign liver tumors
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, hypercholesterolemia, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations containing 0.05 mg or higher of estrogen. The effects of long term use with lower dose formulations of both estrogens and progestogens remain to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease. Relative risk, the *ratio* of the incidence of a disease among oral contraceptive users to that among non-users cannot be assessed directly from case control studies, but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6. The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women 35 or older, with smoking accounting for the majority of excess cases.

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors for coronary artery disease, such as hypertension, diabetes, hyperlipidemias, hypercholesterolemia, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and impair oral glucose tolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see **WARNINGS,** section 9). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. One cohort study has shown the relative risk to be somewhat lower, about 3 for new cases (subjects with no past history of venous thrombosis or varicose veins) and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A 2- to 6-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery and during and following prolonged immobilization. Since the immediate postpartum period also is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular diseases

An increase in both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. In general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users for both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk also is greater in women 35 or older and among smokers.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with some progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content that produces satisfactory results for the individual.

e. Persistence of risk of vascular disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. Subarachnoid hemorrhage also has a significantly increased relative risk after termination of use of oral contraceptives. However, these studies were performed with oral contraceptive formulations containing 0.05 mg or higher of estrogen.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. However, smokers 35 and older and non-smokers 40 and older who use oral contraceptives have an increase in mortality greater than those using other methods of birth control. These facts must be weighed in conjunction with failure rates for other methods and the risk associated with subsequent pregnancy.

3. CARCINOMA OF THE BREAST AND REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone study also showed no latent effect on the risk of breast cancer for at least a decade following long term use. A few studies have shown a slightly increased relative risk of developing breast cancer, although the methodology of these studies, which included differences in examination of users and non-users and differences in age at start of use, has been questioned.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast or cervical cancers, a cause and effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is less than 1 per 1,000,000 users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. More recent studies do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to impair oral glucose tolerance. Oral contraceptives containing greater than 0.075 mg of estrogen cause glucose intolerance with impaired insulin secretion, while lower doses of estrogen may produce less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS,** sections 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives. The incidence of risk also was reported to increase with continued use and among older women. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. PHYSICAL EXAMINATION AND FOLLOW-UP

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines.

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. CARCINOGENESIS

See **WARNINGS** section.

10. PREGNANCY

Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

INFORMATION FOR THE PATIENT

See **PATIENT LABELING.**

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section):

• Thrombophlebitis • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas, carcinomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

• Mesenteric thrombosis • Retinal thrombosis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

• Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema • Melasma which may persist • Breast changes: tenderness, enlargement, secretion • Change in weight (increase or decrease) • Change in cervical erosion and secretion • Diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine • Rash (allergic) • Mental depression • Reduced tolerance to carbohydrates • Vaginal candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

• Pre-menstrual syndrome • Cataracts • Changes in appetite • Cystitis-like syndrome • Headache • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Vaginitis • Porphyria • Impaired renal function • Hemolytic uremic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:

• Increased menstrual cycle regularity • Decreased blood loss and decreased incidence of iron deficiency anemia • Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:

• Decreased incidence of functional ovarian cysts • Decreased incidence of ectopic pregnancies

Effects from long-term use:

• Decreased incidence of fibroadenomas and fibrocystic disease of the breast • Decreased incidence of acute pelvic inflammatory disease • Decreased incidence of endometrial cancer • Decreased incidence of ovarian cancer

Rev. August 1989

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Serious as well as minor side effects have been reported following the use of all oral contraceptives. These include thromboembolic disease. Please see adjacent page for brief summary of prescribing information. © 1990 Syntex Laboratories, Inc. 814-62-116-89

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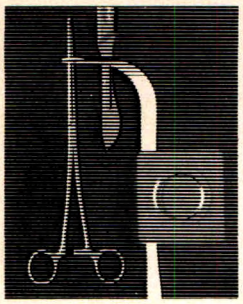
(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, Briceland LL, Cooper B. The conversion of cefoxitin usage to cefotetan: an interdisciplinary approach. *Am J Surg.* 1988; 155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT. Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg.* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference.* ed 43. Oradell, NJ: Medical Economics Co; 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH. Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg.* April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, Outman WR, Deckers PJ, Martens MG. Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg.* 1988;155(5A):67-70. **7.** Centers for Disease Control. 1989 Sexually Transmitted Diseases Treatment Guidelines. *MMWR.* 1989;38(suppl S-8):1-43.

Please see adjacent page for brief summary of prescribing information.

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Count on

CEFOTAN® IM/IV

(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus.**
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.9 × value for males

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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β-Adrenergic receptor blockade in the management of pregnant women with mitral stenosis 37

Saad M. Al Kasab, FRCP, Taher Sabag, MD, Muayed Al Zaibag, FRCP, Mohamed Awaad, MRCOG, Issam Al Bitar, MD, Murtada A. Halim, MRCP, Moheeb A. Abdullah, MRCP, Maie Shahed, MRCP, Vijayaraghavan Rajendran, MRCP, and William Sawyer, MB, ChB

Riyadh, Saudi Arabia

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Gene Burkett, MD, Emmalee S. Bandstra, MD, Jay Cohen, MD, Bernard Steele, MD, and Diana Palow, RN

Miami, Florida

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A. Bardeguez, MD, M. Chatterjee, MD, M. Tepedino, MD, and B. Sicuranza, MD

Newark, New Jersey

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Christos G. Hatjis, MD, Alexander D. Kofinas, MD, James P. Greelish, BA, Melissa Swain, RN, and James C. Rose, PhD

Winston-Salem, North Carolina, and Columbus, Ohio

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Philippe Jeanty, MD, PhD, Donna Kepple, RDMS, Pericles Roussis, MD, and Dinesh Shah, MD

Nashville, Tennessee

The prenatal diagnosis of an aneurysm of the vein of Galen by ultrasonography is demonstrated.

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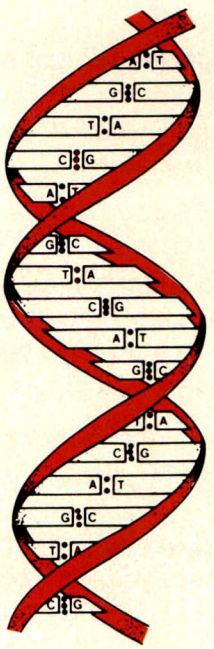
Yukio Manabe, MD, and Yoshinobu Yoshida, MD

Kyoto and Shiga, Japan

In our morphologic study, collagenous tissue in the amnion was not dissociated by prostaglandin treatment in contrast with that in the uterine cervix.

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Columbus, Ohio

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New York, New York

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Chang-Hyun M. Choi, MD, and James R. Pritchard, DO
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Lawrence D. Odom, MD, Leo Plouffe, Jr., MD, CM, and William J. Butler, MD
Augusta, Georgia, and Albany, New York

Two cases of exposure to 5-fluorouracil in the periconceptual period with normal neonatal outcomes are presented.

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To be continued...



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‡Data on file, Ortho Pharmaceutical Corporation.

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San Francisco, California

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Siri L. Kjos, MD, Thomas A. Buchanan, MD, Jeffrey S. Greenspoon, MD, Martin Montoro, MD, Gerald S. Bernstein, MD, and Jorge H. Mestman, MD
Los Angeles, California

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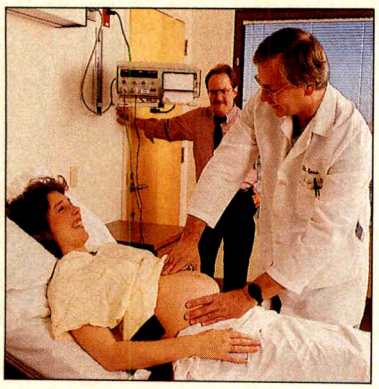
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C. Andrew Combs, MD, PhD, Patricia A. Robertson, MD, and Russell K. Laros, Jr., MD
San Francisco, California

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San Rafael/Petaluma — OB/GYN services are available at both the San Rafael Medical Center and the new Petaluma medical offices, which opened in January of 1989.

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Stanford and Santa Clara, California

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Pittsburgh, Pennsylvania, Baltimore, Maryland, Boston, Massachusetts, San Antonio, Texas, Burlington, Vermont, Seattle, Washington, and Minneapolis, Minnesota

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New York and Bronx, New York

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Bethesda, Maryland, Atlanta, Georgia, and Guatemala, Guatemala

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Seattle, Washington, and Madison, Wisconsin

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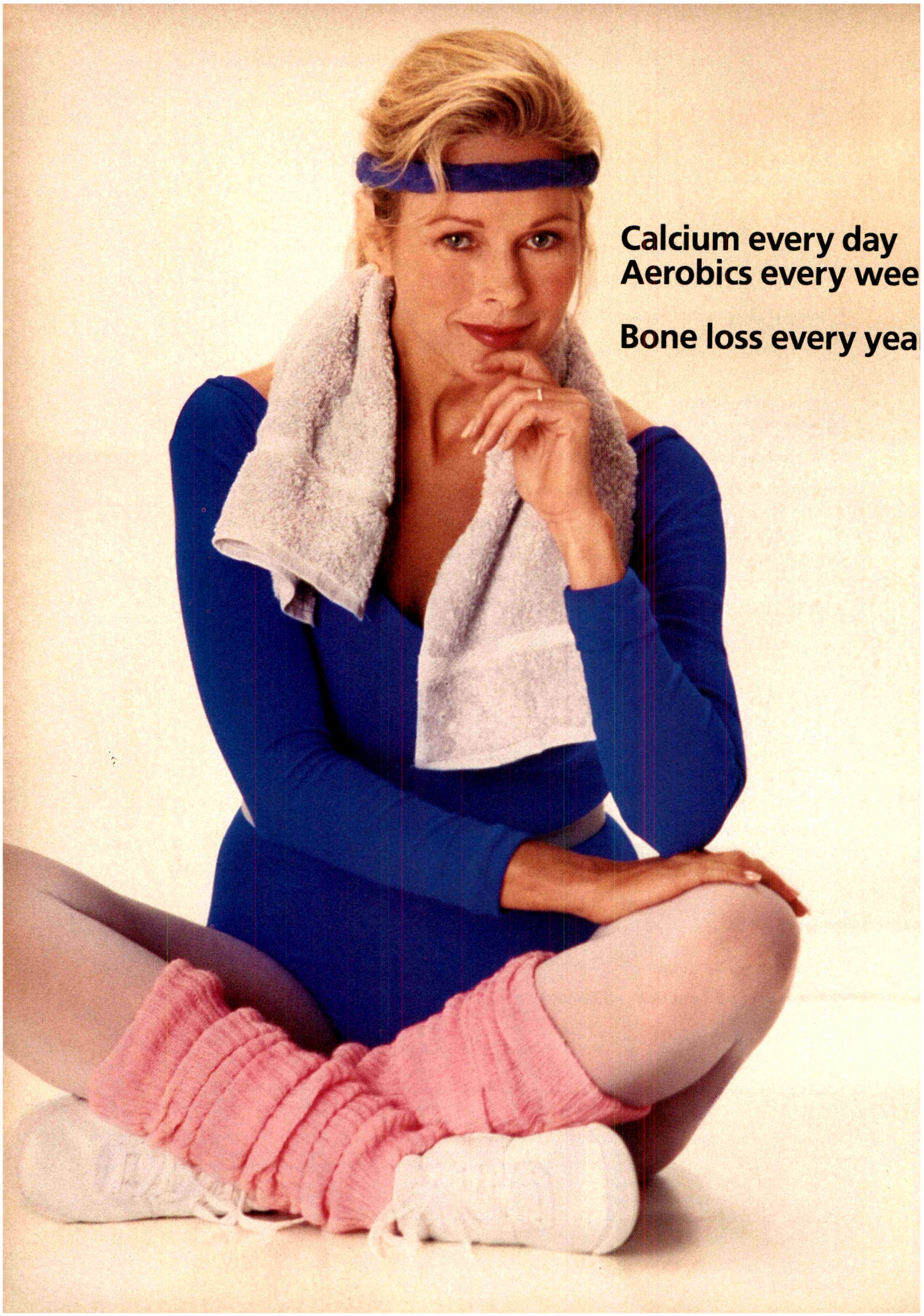
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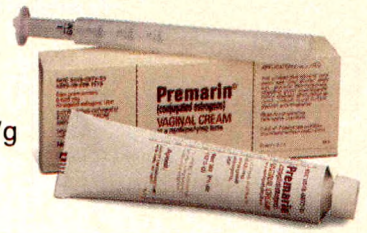
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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULARS.)*

PREMARIN® Brand of conjugated estrogens tablets, USP
PREMARIN® Brand of conjugated estrogens Vaginal Cream, in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures including endometrial sampling when indicated should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY. Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the male and female fetus, an increased risk of vaginal adenosis, squamous-cell dysplasia of the uterine cervix, and vaginal cancer in the female later in life. The 1985 DES Task Force concluded that women who used DES during their pregnancies may subsequently experience an increased risk of breast cancer. However, a causal relationship is still unproven, and the observed level of risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion.

DESCRIPTION: PREMARIN (conjugated estrogens, USP) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters. Tablets are available in 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths of conjugated estrogens. Cream is available as 0.625 mg conjugated estrogens per gram.

INDICATIONS AND USAGE: Moderate-to-severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.) Prevention and management of osteoporosis (abnormally low bone mass). Atrophic vaginitis. Atrophic urethritis. Hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

PREMARIN (conjugated estrogens) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected pregnancy (see Boxed Warning). 2. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 3. Known or suspected estrogen-dependent neoplasia. 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. Estrogen replacement therapy has not been reported to increase the risk of thrombophlebitis and/or thromboembolic disease. However, there is insufficient information regarding women who have had previous thromboembolic disease.

PREMARIN Tablets and Vaginal Cream should not be used in patients hypersensitive to their ingredients.

WARNINGS: Some studies suggest a possible increased incidence of breast cancer in women taking higher doses of estrogen for prolonged time periods. The majority of studies have not shown an association with usual estrogen replacement doses. Endometrial cancer risk among estrogen users was about 4-fold or greater than in non-users, and appears dependent on treatment duration and estrogen dose. In patients on combined estrogen-progestin therapy, this risk appears to be decreased. (See PRECAUTIONS below.)

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders.

A 2.5-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens has been reported.

Large doses of estrogen such as those used to treat prostate and breast cancer have been shown to increase the risk of non-fatal myocardial infarction, pulmonary embolism, and thrombophlebitis in men. This cannot necessarily be extrapolated to women. However, to avoid theoretical cardiovascular risk caused by high estrogen doses, the doses for estrogen replacement therapy should not exceed the recommended dose.

Blood pressure should be monitored with estrogen use, especially if high doses are used.

Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: The addition of a progestin for 7 or more days of a cycle of estrogen administration reportedly lowers the incidence of endometrial hyperplasia. Studies of endometrium suggest that 10 to 13 days of progestin are needed to provide maximal endometrial maturation and elimination of hyperplastic changes. Additional risk, such as adverse effects on carbohydrate and lipid metabolism, may be associated with the inclusion of progestin in estrogen replacement regimens. The choice of progestin and dosage may be important in minimizing these adverse effects.

Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding and mastodynia. Pre-existing uterine leiomyomata may increase in size during estrogen use. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, or metabolic bone diseases associated with hypercalcemia.

The following drug/laboratory test interactions have been reported, some only with estrogen-progestin combinations (oral contraceptives):

1. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
2. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by T_4 levels determined by column or by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered.
3. Impaired glucose tolerance.
4. Reduced response to metyrapone test.
5. Reduced serum folate concentration.

MUTAGENESIS AND CARCINOGENESIS: Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver.

PREGNANCY CATEGORY X: Estrogens should not be used during pregnancy. See **CONTRAINDICATIONS** and Boxed Warning.

NURSING MOTHERS: As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy; changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine fibromyomata, vaginal candidiasis, change in amount of cervical secretion; tenderness or enlargement of breasts; nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice; chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature, intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea and vomiting.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of conjugated estrogens tablets, USP

1. *Given cyclically for short-term use only.* For treatment of moderate-to-severe vasomotor symptoms, atrophic vaginitis, or atrophic urethritis associated with the menopause (0.3 mg to 1.25 mg or more daily). The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (eg, three weeks on and one week off). Attempts to discontinue or taper medication should be made at three- to six-month intervals.
2. *Given cyclically:* Hypoestrogenism. Osteoporosis.

Hypoestrogenism due to: Female hypogonadism—2.5 mg to 7.5 mg daily in divided doses for 20 days followed by 10 day rest period. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. Female castration or primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis—0.625 mg daily. Administration should be cyclic (eg, three weeks on and one week off).

PREMARIN® Brand of conjugated estrogens Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Attempts to discontinue or taper medication should be made at three- to six-month intervals.

Usual dosage range: 2 g to 4 g daily, intravaginally, depending on the severity of the condition.

Patients with an intact uterus who are treated with either PREMARIN Tablets or Vaginal Cream should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

Revised August 21, 1989

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General requirements for preparation of manuscripts

The original and two good-quality photocopies of the manuscript and three sets of glossy prints of illustrations are required.

Manuscripts must be typed double-spaced on one side only of 22 × 28 cm (8½ × 11 inch) white bond paper with 1-inch margins at top, bottom, and sides. Number pages consecutively in the upper right-hand corner in the following order: title page, condensation, abstract, body of text, acknowledgments, references, legends, and tables.

Title page. The title page (page 1) should contain in sequence the title (concise and suitable for indexing purposes); author line with first name, middle initial, and last name of each author and each author's highest academic degree (both MD and PhD are acceptable); city(ies), state(s) in which the study was conducted; divisional, or departmental, and institutional affiliations at the time the study was performed; source(s) of financial support; presented line, if applicable; disclaimers, if any; name, address, and business and home telephone numbers of author to whom requests for reprints should be addressed (if reprints will not be available, it should be so stated); and name, address, and business and home telephone numbers of author responsible for correspondence concerning the manuscript if different from author to whom reprint requests are addressed. At the bottom of the title page supply a short title for the running head not exceeding 52 characters (including word spaces).

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Abstract page and key words/phrases. On manuscript page 3 type the abstract, double-spaced, with the required margins and headed by the title of the article and name(s) of author(s). Abstracts for regular articles, Current Investigation, Clinical Opinion, and Current Development may not exceed 150 words. Abstracts for case reports and brief communications may not exceed 50 words. Below the abstract list 3 to 5 *key words* or short phrases for indexing purposes.

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Only standard abbreviations are to be used. Consult the *Council of Biology Editors Style Manual* or the AMA's *Manual for Authors and Editors.* Abbreviations in the title are not acceptable. They should be avoided, if possible, in the abstract. In the text they should be kept to a practical minimum. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

Either the generic, chemical, or proprietary names of drugs may be used. If the generic or chemical name is used, authors may, if they desire, insert the proprietary name in parentheses after the first mention in the text, with the name of the manufacturer and city and state.

Regular articles are customarily organized into the following sections: an introduction and headings that identify Material and Methods, Results, and Comment. Authors may wish to summarize their findings in a short paragraph at the end of the Comment section. This format may not be appropriate for some types of articles.

In the introduction, state concisely the purpose and rationale for the study and cite only the most pertinent references as background.

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Estimating length of manuscripts

The length of text material (introduction through Comment section) in regular manuscripts accepted for publication normally ranges from 750 to 4200 words (an average of 2000 words). A 4200-word text can seldom be accepted, especially if tables and figures are included. The average manuscript of 2000 words of text with abstract, 3 tables with captions, 2 figures with legends, and references makes a 5.7-page article in the JOURNAL. The 2000 words of text alone make approximately 8 pages of manuscript typed double-spaced with the required 1-inch margins (approximately 250 words per page). A table or figure that occupies both columns of half a JOURNAL page is equivalent to approximately 500 words in manuscript. Thus, if a greater number of illustrations and tables are used, the length of the text should be adjusted accordingly.

In the *Results* section present the detailed findings. Include mentions of all tables and/or figures. Avoid duplication of text and supporting material. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the Comment section.

In the *Comment* section state the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your findings with those of others. No new data should be presented in this section.

Acknowledgments. Acknowledge only persons who have made substantive contributions to the study.

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Illustrations and tables. Illustrations and tables should supplement, not duplicate, the text; presentation of data in either one or the other will suffice.

A reasonable number of halftone and line illustrations will be reproduced without charge, but special arrangements must be made with the Editors for *color illustrations* at a cost of $525 per page (one side).

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Both the checklist and the copyright statement forms **must be completed** and sent with each submitted manuscript. If **not** completed, these forms will be returned to the author for completion.

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—The original and two copies of the manuscript are submitted.
—The appropriate signed completed checklist and assignment of copyright signed by **all** authors accompany the manuscript.
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—Human experimentation has been approved by the local institution as stated in the Methods section.
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—The covering letter with essential information is with the manuscript.
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—Three to five key words or short phrases are placed beneath the abstract on page 3.

Tables

—Each table headed by a caption and numbered in Roman numerals is typed double-spaced on a separate page.
—Tables are cited in sequence in the text.

Figures

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AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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IN BRIEF:

Indications and Usage—LO/OVRAL* is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions:

1. Thombophlebitis or thromboembolic disorders.
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral-vascular or coronary-artery disease.
4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia.
6. Undiagnosed abnormal genital bleeding.
7. Known or suspected pregnancy (see Warning No. 5).
8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exits, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 [ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000], risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders [e.g., thombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis]. Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained elevated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI persisted for at least 9 years in women 40- to 49-years-old who had used OC's for 5 or more years. Findings in both studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polysystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with the use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests.

As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, hemolytic uremic syndrome.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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CLINICAL SECTION

Clinical Opinion

Safe motherhood: Cesarean section or symphysiotomy?

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The place of symphysiotomy in the management of cephalopelvic disproportion is discussed on the basis of the existing literature, reviewing maternal mortality and morbidity after symphysiotomy and the vaginal delivery rate in a subsequent pregnancy after a previous symphysiotomy. These are compared with the outcome of cesarean section performed in similar circumstances. (AM J OBSTET GYNECOL 1990;163:1-4.)

Key words: Cesarean section, symphysiotomy, maternal mortality, subsequent vaginal delivery

At least 500,000 women die annually from the complications of abortion, pregnancy, and labor, and only recently maternal mortality has been recognized by the international community as a serious public health concern.[1-2] The World Health Organization, in collaboration with the United Nations Population Fund and the World Bank, in 1987 launched the "Safe Motherhood Campaign" to combat this appalling situation.

Apart from abortion, obstructed labor is one of the leading conditions on the road to maternal death. In a report from the World Health Organization[3] cesarean section was advocated in addition to other measures to reduce mortality resulting from obstructed labor.

On the other hand, cesarean section itself carries mortality and morbidity risks, especially in the conditions that prevail in the rural areas of developing countries where obstructed labor is most prevalent. The maternal mortality rate after cesarean section in different African hospitals is 1.8% (range, <0.6% to 5.0%) with approximately 3% in rural and 1% in teaching hospitals (Table I).[4] The mortality rate after cesarean section in women booked for delivery in a Nigerian teaching hospital (0.6%) is still six times higher than the mortality rate after cesarean section at present in the Western world (0.1%).[5-6] Even lower mortality rates have been reported in the United States: six per 10,000 operations.[7] On the other hand, serious underreporting of maternal deaths after cesarean section has been detected as well.[8]

One remote risk concerns rupture of the uterine scar in a subsequent pregnancy, and this is a rather frequent complication that often leads to perinatal death and serious maternal morbidity and even mortality (Table I).

Symphysiotomy has been proffered as an alternative to cesarean section in some cases of obstructed labor. Symphysiotomy is the artificial separation of the symphysis pubis with a scalpel to enlarge the pelvic diameters to facilitate the process of birth. It has never become popular because of its urologic and orthopedic complications and is viewed as an out-of-date or second-class obstetric intervention in the Western world and even among the medical profession in Third World countries. However, experience with the procedure does not warrant such a negative attitude and as an illustration recent data on mortality and morbidity after symphysiotomy are presented in this article.

Maternal mortality after symphysiotomy at present is almost negligible; in a series of 1752 symphysiotomies only three women died and none of these deaths was related to the symphysiotomy procedure (Table I). Two women died from eclampsia and one death occurred after cesarean section when symphysiotomy failed to deliver the baby.

In that series of 1752 symphysiotomies, serious ma-

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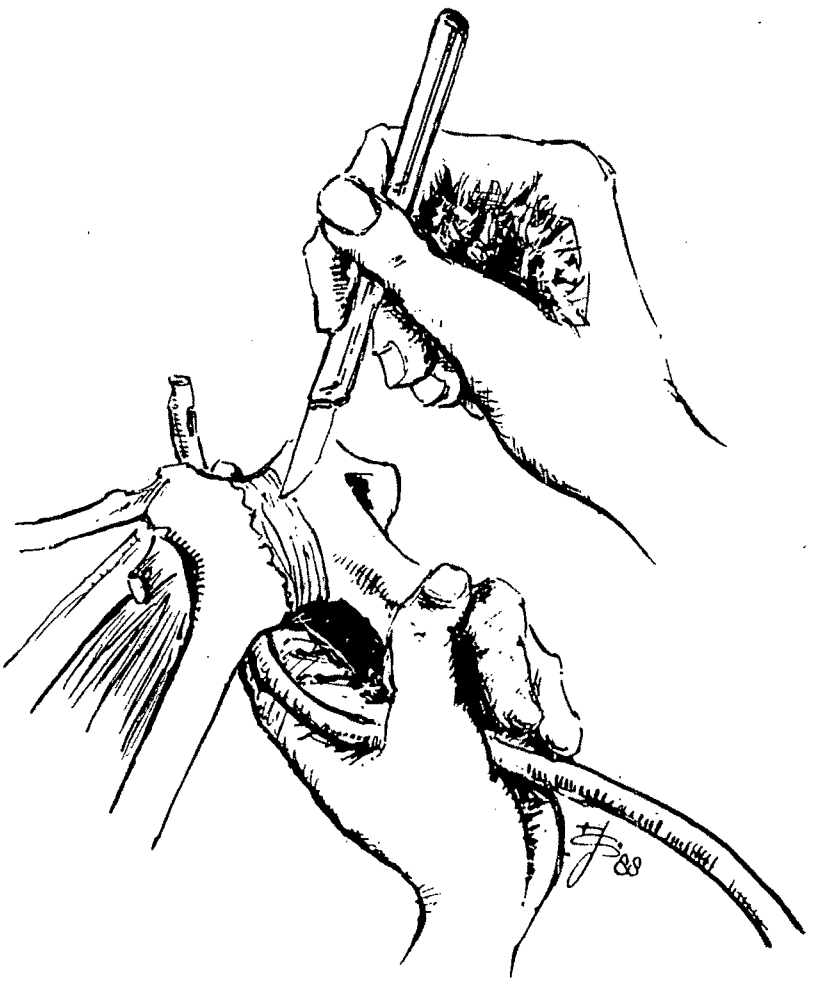


Fig. 1. Insertion of urinary catheter during procedure of symphysiotomy.

ternal morbidity included 30 vesicovaginal fistulas (1.7%), 33 lesions of the anterior vaginal wall including the urethra (1.9%), 10 cases of osteitis pubis–retropubic abscess (0.6%), 32 women with long-term walking difficulties or pain (1.8%), and 36 with stress incontinence (2.1%).[9] More than one complication often occurred in one woman. Therefore the number of women affected is less than the number of 141 complications (8.1%). Fifteen of the 30 fistulas appeared to be a result of pressure-necrosis of the bladder neck because of obstucted labor rather than because of symphysiotomy. The latter fistulas develop immediately after birth, whereas those that are a result of obstructed labor only develop some days after delivery when necrotic tissue is shed.

A previous symphysiotomy is said to cure cephalopelvic disproportion, and the outcome of subsequent labor in women with a history of previous symphysiotomy shows an 87% vaginal delivery rate. In only one study two cases of rupture of an unscarred uterus were reported after a previous symphysiotomy.[9]

It is not intended within the scope of this article to dwell on the technique of the procedure, which is explained in the existing literature.[10-11] However, a few remarks will be made here. The complication rate can be lowered by strict adherence to a protocol, and the rules provided by Gebbie[12] in 1974 are generally accepted. A symphysiotomy should be performed only when one third or more of the fetal head has entered the pelvic brim, the fetal head is not felt prominent in front of the symphysis, and cervical dilatation is >7 cm.

Second, some of the immediate fistulas or vaginal wall lacerations were a result of performing the procedure without the insertion of a urinary catheter; others were a result of the application of forceps after symphysiotomy. The insertion of a urinary catheter should never be omitted (Fig. 1) and the use of forceps is contraindicated. Instead, the vacuum extractor can be applied after symphysiotomy has been performed.[13]

Comparison of the results of symphysiotomy with those of cesarean section for cephalopelvic disproportion (the best possible control when randomization is

Table I. Cesarean section and symphysiotomy in Africa*

	Cesarean section (n = 8446)			*Symphysiotomy (n = 1752)*	
	No.	*%*	*Range*	*No.*	*%*
Maternal deaths	151	1.8	0.6 – 5.0	3	0.2
	Previous cesarean section		(n = 7018)	Previous symphysiotomy	(n = 229)
Uterine rupture	271	3.9	0.3 – 6.8	2	0.9
Repeat cesarean section	3482	50	30 – 80	25	11

*Source: van Roosmalen.[4]

Table II. Comparison of outcome of symphysiotomy and cesarean section for cephalopelvic disproportion in rural Tanzania, 1976 to 1983*

	Symphysiotomy (n = 54)		*Cesarean section because of cephalopelvic disproportion (n = 100)*	
	No.	*%*	*No.*	*%*
Maternal mortality	0	0	5	5
Serious maternal morbidity	4	7	6	6
Perinatal mortality	11	20	13	13
	Previous symphysiotomy	(n = 229)	Previous cesarean section because of cephalopelvic disproportion	(n = 64)
Vaginal delivery rate	199	87	28	44

*Source: van Roosmalen.[4,7]

difficult) indicates less mortality risk for the mother, whereas maternal morbidity, although different in nature, does not differ much in frequency (Table II). The vaginal delivery rate after a previous symphysiotomy (87%) is much higher than that after cesarean section for disproportion (44%).[4] The need for blood transfusion with its risks related to acquired immunodeficiency syndrome is much less after symphysiotomy than after cesarean section.[14]

Comment

Symphysiotomy deserves a place in the management of cephalopelvic disproportion. The fact that symphysiotomy is not practiced at present in Western countries does not make this operation second-class or outdated in the greatly differing circumstances of Third World counties in which cesarean birth is generally disliked and carries great maternal risks of mortality and serious morbidity, especially when performed in advanced labor.[15-16] Two recent cases of symphysiotomy have been reported from Great Britain when there was unexpected pelvic entrapment of the aftercoming head of a breech infant.[17] In the American literature a recent plea was made for symphysiotomy in the management of serious shoulder dystocia.[18-19] However, in such emergency cases much expertise should be available to safely perform the procedure. This will seldom be the case.

But in selected cases of obstructed labor in developing countries, symphysiotomy is a relatively simple and rapid procedure to facilitate delivery, and can be regarded as an example of appropriate technology. It leaves the uterus unscarred and thereby diminishes the risk of future uterine rupture. Furthermore, it fulfills the sociocultural needs to achieve vaginal delivery in areas in which cesarean birth is a much disliked option, involving a woman's disgrace in failure to give birth in the normal way.[20] Fear of getting another cesarean section after a previous operation once caused a woman to abscond from the hospital. She died undelivered at home, possibly because of scar rupture.

From this review it is concluded that the adverse effects of symphysiotomy have been greatly exaggerated.[21-22] However, more research into the late sequelae of symphysiotomy should be undertaken in the rural areas of Third World countries. One such study is in progress in Zaire.[14]

The help of J. Stouten in drawing the figure is kindly acknowledged.

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Cost-effectiveness of intrapartum screening and treatment for maternal group B streptococci colonization

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Early-onset neonatal group B streptococci infection occurs in two cases per 1000 live births in the United States and is associated with a mortality rate >20%. Nearly 30% of infected infants have concomitant meningitis and half suffer permanent neurologic damage. Group B streptococci also account for at least 20% of postpartum metritis. The annual cost of group B streptococci infection in the United States is conservatively estimated at nearly 2000 neonatal deaths and >$500 million, excluding the costs of long-term neurologic handicaps. Intrapartum chemoprophylaxis with ampicillin is effective in curtailing transmission of group B streptococci from mother to infant. Methods have been developed to identify maternal colonization before delivery. We applied principles of decision analysis to evaluate cost-effectiveness of intrapartum screening for maternal group B streptococci colonization with various reported methods in cohorts of low- and high-risk women. In the United States intrapartum screening for group B streptococci is cost-effective and offers the potential to avert a significant number of neonatal deaths and postpartum infections. (AM J OBSTET GYNECOL 1990;163:4-8.)

Key words: Group B streptococcus, rapid screening, chemoprophylaxis, cost effectiveness

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Early-onset group B streptococci infections are a serious cause of morbidity and mortality in neonates, with an incidence of two to three cases per 1000 live births in the United States[1, 2] and a mortality rate of 20% to 30%.[2] It has been estimated that >2000 infants die from these infections each year in the United States. A survey of infants with neonatal sepsis found that group B

streptococci were the etiologic organisms in 41% of cases.[3] In terms of the economic impact of hospital treatment and the long-term management of neurologic sequelae, group B streptococci were the fourth most important cause of potentially preventable infectious morbidity in the United States.[2] The National Academy of Sciences has estimated that the cost of total disease from early-onset neonatal disease and obstetric disease exceeded $500 million in 1985.[2]

Numerous approaches to reduce the devastating toll exerted by these infections have been investigated, including immunotherapy and prophylactic antibiotics.[1] Three general methods of antibiotic prophylaxis against neonatal group B streptococci disease have been studied:

1. Antepartum treatment of pregnant women colonized with group B streptococci in the third trimester achieves a marked but transient reduction in colonization, but by term the colonization rate returns to pretreatment levels.[4] The high prevalence (up to 30% of pregnant women), the intermittent nature of the carrier state, and the high recurrence rate mitigate against cost-effectiveness of antepartum prophylaxis.[5]

2. Prophylactic treatment of all exposed neonates shortly after birth has produced mixed results.[6] In addition, infections with penicillin-resistant organisms increased among treated infants. Therefore routine use of penicillin prophylaxis is currently not recommended for exposed but asymptomatic neonates.

3. However, intrapartum treatment of colonized women has been shown to significantly and consistently reduce early-onset group B streptococci infections and mortality.[7-11] Two investigator groups[12, 13] have addressed the cost-effectiveness of such therapy—a consideration that is separable from the question of efficacy. These reports provide compelling arguments in favor of intrapartum prophylaxis, although the analysis of Boyer[12] was based on prenatal cultures as a means to predict colonization at presentation in labor, and Minkoff[13] proposed intrapartum cultures of only high-risk women. Both of these approaches may potentially overlook a significant number of parturients and neonates at greatest risk for group B streptococci disease. It is possible that these analyses may have underestimated the potential value of screening and prophylaxis.

Since the publication of these reports, several sensitive techniques have been developed to allow rapid detection of group B streptococci colonization.[14-18] Thus the potential exists to quickly and accurately identify women in labor who are colonized by group B streptococci and to initiate intrapartum antibiotic therapy in sufficient time to interdict neonatal, and possibly maternal, infections.

With the use of the methods of decision analysis we attempted to determine which populations of patients may benefit from intrapartum prophylaxis, how sensitive the analysis is to changes in test accuracy and costs of screening and treatment, and what the annual costs of such a program would be in the United States.

Table I. Baseline assumptions in the decision tree

Assumption	
Cost of screening test	$20[12]
Cost of treating colonized mothers	$200[12]
Cost of treating infected neonate	$22,000[12]
Probability of neonatal infection if mother colonized in labor	0.02[21-25]
Probability of neonatal death if infected	0.20[9, 21-25]

Material and methods

Decision analysis is a schematic process for examination of problems that require one or more decisions and that result in more than one outcome.[19] The analysis consists of four basic components: (1) the decision tree is a flow diagram that specifies alternative courses of actions and possible outcomes of these actions; (2) branch points in the decision tree are called chance nodes; an associated probability at each node is estimated from the medical literature; (3) relative values, expressed in units such as costs or deaths, are assigned to all outcomes; (4) the score for each decision alternative is calculated by multiplying the relative value for each outcome by the probability of its occurrence and adding relative value scores across all branches of the decision tree.

The decision tree used in this analysis is shown in Fig. 1. The baseline assumptions used in this analysis and the references from which the numbers were obtained are listed in Table I. Treatment of neonates born to colonized mothers was not considered separately in the cost analysis. However, the cost of antibiotic therapy referenced in Table I was taken from the study of Boyer,[12] the one group that continued prophylactic antibiotics into the neonatal period. Data from the other two groups would support not administering antibiotics to the neonates unless clinically indicated. A computer program written in QUICK BASIC computer language (Microsoft Corp., Redmond, Wash.) was used to calculate outcomes for various branch probabilities and relative values in the tree.

The performance parameters of test procedures reported to identify group B streptococci colonization are listed in Table II. Only those screening tests that allow detection in <2 hours were considered for this analysis.

Sensitivity analysis is a process in which the probabilities, relative values, or other parameters in a prob-

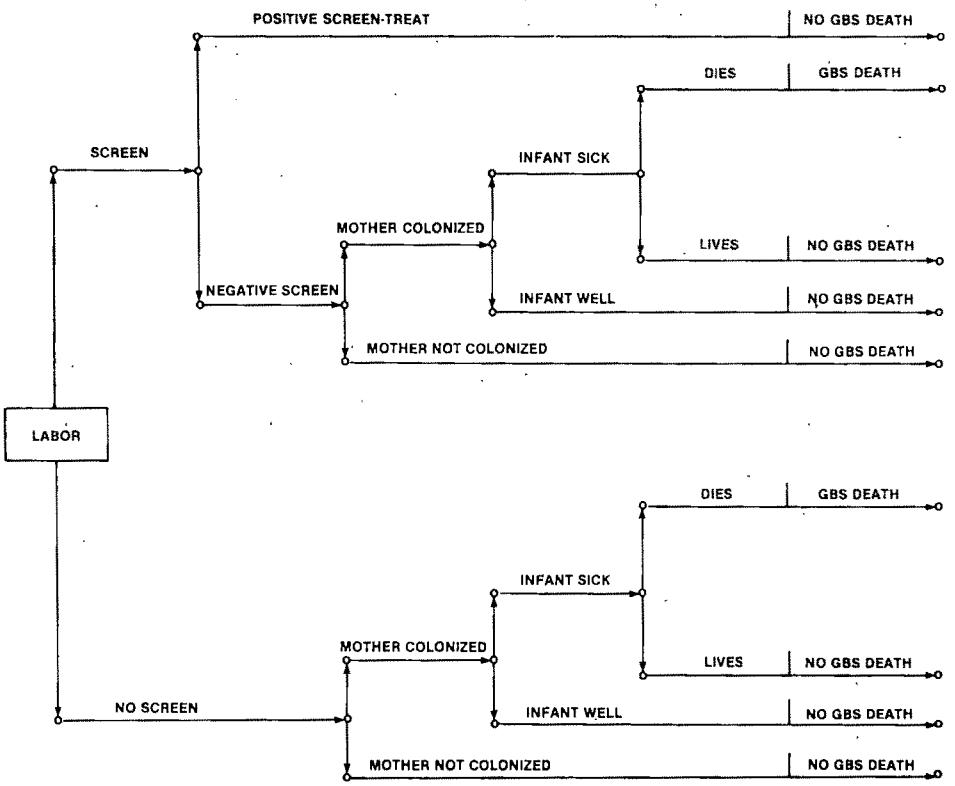


Fig. 1. Decision tree for analysis of cost effectiveness of intrapartum screening and treatment for group B streptococci colonization.

Table II. Performance of rapid screening tests for group B streptococci

Reference	*Method*	*Sensitivity (%)*	*Specificity (%)*	*Negative predictive value (%)*	*Prevalence (%)*
Sandy[14]	Gram stain	38	61	86	14
Isada[15]	Latex	57.9	93.2	98	4.4
Brady[16]	Latex	88	99.6	99.4	5
Holls[17]	Gram stain	93	69	98	14.3
Feld[17-8]	Gram stain	100	66.7	100	12.5

Only methods that yielded results in <2 hours are reported.

lem are varied to determine whether changes in them would affect the decision. In this case we determined the sensitivity of cost and survival to changes in the prevalence of colonization and the sensitivity and specificity of the screening test.

Results

The effects of intrapartum screening and treatment of group B streptococci colonization are shown in Table III. The effects on cost and survival ratios of varying test sensitivity and specificity are calculated for a range of prevalences. It is readily apparent that the extra costs of screening vary significantly with test sensitivity and specificity as well as colonization prevalence, although survival ratios depend only on test performance.

Survival ratios can exceed 1.0 even for relatively poor test parameters, although at low prevalences the average cost to avert one early neonatal death may be extremely high. For instance, with use of the procedure reported by Isada[15] in a population with a colonization rate of only 1% would require an average cost of $1.38 million to save one infant. However, in a cohort colonized at a rate of 20% the cost would be only $6700 per infant saved.

Comment

Screening is generally defined as "the presumptive identification of a disease or defect by the use of an examination or test procedure that can be applied rapidly, easily, and relatively inexpensively.[20] The goal of

Table III. Sensitivity analysis: effect of colonization prevalence and quality of screening tests on neonatal survival and cost-effectiveness of intrapartum screening and treatment of group B streptococci colonization

Prevalence (%)	*SCOST ($)*	*UCOST ($)*	*Survival ratio**	*Cost ratio**	*Survival cost† ($)*
Method of Isada‡					
1	36.70	4.40	2.4	8.3	1. 8 M
5	47.97	22.00	2.4	2.2	224 K
10	62.34	44.00	2.4	1.4	79 K
20	91.09	88.00	2.4	1.04	7 K
Hypothetical§					
1	42.28	Same	5.0	9.6	1.2 M
5	51.40	as	5.0	2.3	183 K
10	62.80	column	5.0	1.4	59 K
20	85.60	above	5.0	0.97	−3.8 K
Method of Brady‖					
1	23.08	Same	8.3	5.3	530 K
5	32.20	as	8.3	1.5	58 K
10	43.6	column	8.3	1.0	−1 K
20	66.40	above	8.3	0.8	−31 K

SCOST, Average cost per screened patient; *UCOST*, average cost per unscreened patient.
*Screened versus unscreened.
†Average cost per neonatal group B streptococci death averted.
‡Sensitivity = 0.579, specificity = 0.932.
§Assumption of sensitivity = 0.8, specificity = 0.9.
‖Sensitivity = 0.88, specificity = 0.996.

screening is to identify persons who have a high likelihood of disease and thus require more diagnostic and usually more expensive confirmatory tests. However, in this analysis the result of the screening test determines which laboring women will be treated with prophylactic antibiotics. The sensitivity and specificity of the screening test incorporate the concept of confirmatory testing with a gold standard, although in a retrospective sense.

Confirmatory gold standards, such as intrapartum cultures are usually available too late to allow for prophylactic treatment. It was for this reason that we elected to consider only screening tests that could be obtained rapidly (<2 hours) and that could be obtained 24 hours a day in even small medical facilities.

From the analysis presented in Table III it appears that significant reduction in early-onset neonatal group B streptococci disease can be accomplished through intrapartum screening and chemoprophylaxis, even with the use of a test with less than optimum performance such as that reported by Isada.[15] However, unless the population at risk has a colonization prevalence >10%, the average cost to save one neonate may be exhorbitant. That determination involves many value judgments because it may be argued that the value of one life is inestimable.

With use of a very high-performance screening test such as reported by Brady et al.[16] invokes very few controversial value judgments. In the U.S. population as a whole, with a group B streptococci prevalence of 10% and a birth rate of 3.5 million, a screening and prophylaxis program with the test reported by Brady could avert 1230 neonatal deaths from group B streptococci annually at a total savings of $1100 per neonatal death averted. In a higher risk population such as women with preterm labor, premature rupture of the membranes, or intrapartum fever, the program could avert seven deaths and save an average of $216,000 for every 10,000 women in the cohort.

We have not considered the possible benefit from the reduction of the incidence of late-onset group B streptococci disease because data on the effectiveness of intrapartum antibiotics on this infection are sparse. Data that do exist but that were also not considered in our cost effectiveness analysis are savings that result from reduced maternal morbidity from group B streptococci and the reduction in costs of long-term neurologic sequelae from early-onset group B streptococci meningitis. These considerations would significantly increase the cost-effectiveness of screening and treatment.

Therefore we conclude that intrapartum screening for group B streptococci with a technique that allows for accurate and rapid ascertainment of colonization before intrapartum maternal chemoprophylaxis can effect a significant reduction in early-neonatal death from group B streptococci in a cost-effective manner. Although the evidence would support the screening of all laboring women in the United States, individual medical centers may use this analysis, applying their own cost estimates and colonization prevalences to de-

termine which cohorts of patients they believe should be screened and treated.

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The effect of adjusting maternal serum α-fetoprotein levels for maternal weight in pregnancies with fetal open spina bifida

A United States collaborative study

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The effect of adjustment of maternal serum α-fetoprotein levels for maternal weight was evaluated in 143 pregnancies associated with fetal open spina bifida. The cases were analyzed with gestational dates as initially assigned either by last menstrual period (73%) or by ultrasonography (27%). The weights of women with pregnancies affected by open spina bifida were found not to be different from unaffected pregnancies. Adjustment resulted in a net increase in detected cases at two commonly used cutoff points: 2.0 and 2.5 multiples of the median. At 2.0 multiples of the median, the detection rate increased from 80% to 84%, whereas at 2.5 multiples of the median the rate rose from 68% to 69%. Adjustment for maternal weight has previously been shown to reduce the false-positive rate in maternal serum α-fetoprotein screening for fetal open spina bifida by reducing variance in unaffected pregnancies; our data provide further support for consideration of maternal weight when interpreting maternal serum α-fetoprotein measurements. (Am J Obstet Gynecol 1990;163:9-11.)

Key words: Maternal weight, α-fetoprotein, open spina bifida

The adjustment of maternal serum α-fetoprotein (maternal serum AFP) levels for maternal weight is known to reduce the variance of distribution of maternal serum AFP levels in pregnancies not affected with fetal open spina bifida without shifting distribution in either direction.[1-3] If similar results were obtained in affected pregnancies, both sensitivity and specificity of maternal serum AFP screening would increase with maternal weight adjustment. This multicenter collaborative study examines for the first time the effect of maternal weight adjustment on a large series of pregnancies affected with fetal open spina bifida.

Methods

Study design. The study design is described elsewhere.[4] Participating centers were limited to those capable of complete ascertainment of pregnancies associated with fetal open spina bifida. Table I lists the participating centers, the number of pregnancies affected with fetal open spina bifida, and the collaborating investigators.

Maternal weight. This analysis was restricted to the 143 cases with reported maternal weights (10 black and 133 white women). In 118 of these, the multiple of the median values reported by the contributing centers had been adjusted for maternal weight. To standardize the analysis of the effect of maternal weight adjustment on the detection of open spina bifida, we first converted the adjusted multiples of the median values to unadjusted values according to each reporting center's own method.[5-7] Weight-adjusted multiples of the median were then calculated with the formula[8]:

$$\text{Weight-adjusted multiple of the median} = \text{Unadjusted multiple of the median} / 10^{(0.2658 - 0.00188 \times \text{Maternal weight in pounds})}$$

Gestational age. The initially assigned gestational age was used in the analysis and was based on last menstrual period in 107 cases and on ultrasonography in 36 cases. Dating by both methods was reported for 105 cases.

From the Foundation for Blood Research. Collaborators are shown in Table I.
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Table I. Participating centers and number of pregnancies with fetal open spina bifida and maternal weight available

*Center**	*No. of pregnancies*
1. Bowman Gray School of Medicine, Winston-Salem, N.C.	29
2. California AFP Screening Program, Berkley, Calif.	27
3. Case Western Reserve University, Cleveland, Ohio	15
4. Eastern Virginia Medical School, Norfolk, Va.	1
5. Foundation for Blood Research, Scarborough, Me.	23
6. Harvard Community Health Plan, Peabody, Mass.	1
7. Regional Medical Genetics Laboratory, Thiells, N.Y.	4
8. Southwest Biomedical Resesarch Institute, Scottsdale, Ariz.	4
9. University of Iowa Hospitals and Clinics, Iowa City, Iowa	4
10. University of North Carolina, Chapel Hill, N.C.	16
11. University of Rochester Medical Center, Rochester, N.Y.	6
12. University of South Florida, Tampa, Fla.	2
13. University of Vermont, Burlington, Vt.	5
14. Womens and Infants Hospital, Providence, R.I.	6
TOTAL	143

*Investigators, by center: *1*, Barbara K. Burton, MD; *2*, George C. Cunningham, MD, and Linda Lusting; *3*, Lois Dickerman, PhD, and Susan M. Lewis; *4*, George L. Wright, Jr., PhD, and Diane N. Brassil; *5*, James E. Haddow, MD, George J. Knight, PhD, and Glenn E. Palomaki; *6*, Bernie Perella; *7*, Lawrence R. Shapiro, MD; *8*, Frederick Hecht, MD, and Linda A. Bradley, PhD; *9*, Roger A. Williamson, MD, and Stanley Grant; *10*, John Seeds, MD, and Lauren Lingley; *11*, Robert A. Mooney, PhD, and Dean A. Arvan, MD; *12*, William F. O'Brien, MD, and Deborah Sternlicht; *13*, Carol J. P. S. Walters, PhD; *14*, Jacob A. Canick, PhD, and Diane Panizza.

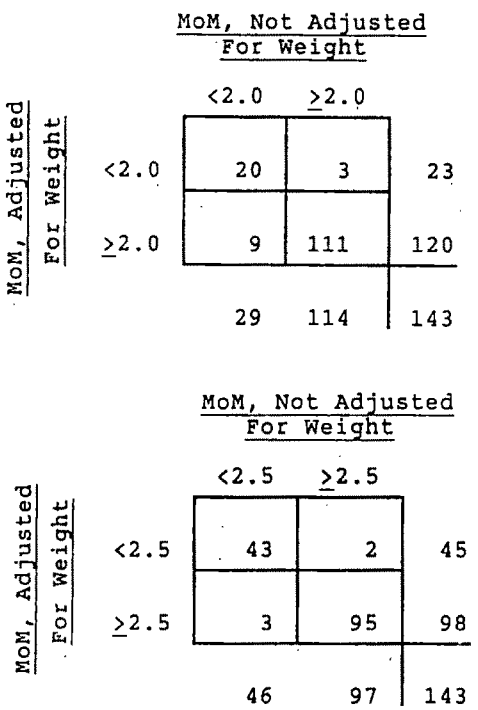


Fig. 1. Effect of adjusting maternal serum AFP for maternal weight on fetal open spina bifida detection at two commonly used cutoff points. This original method of gestational age assignment was based on last menstrual period in 107 cases and ultrasonography in 36. *MoM*, Multiples of the median.

Results

The median maternal serum AFP multiple of the median for the 143 affected pregnancies was 3.39 before weight adjustment and 3.41 after weight adjustment, and variance of the $\log_{10}$ transformed distribution was reduced by 0.0030 (from 0.0640 to 0.0610).

The effect of maternal weight adjustment on open spina bifida detection at two commonly used cutoffs, 2.0 and 2.5 multiples of the median, is shown in Fig. 1. Weight adjustment results in a net increase in detection of six cases with the 2.0 multiple of the median cutoff (three cases lost, but nine additional cases gained), raising the detection rate from 80% to 84%. With the 2.5 multiple of the median cutoff, there is a net increase of one case (two cases lost, but three additional cases gained) with weight adjustment, raising the detection rate from 68% to 69%. Similar slight increases or no overall changes in the detection rates are also obtained using the 128 cases with dating by last menstrual period or the 117 cases with dating by ultrasonography. In the former group, at a cutoff of 2.0 multiples of the median, the detection rate increases from 75% to 82% after weight adjustment, whereas the detection rate remains constant at 63% with the use of 2.5 multiples of the median as a cutoff. In the latter group, no overall changes occur in the detection rates of 90% and 80% for cutoffs of 2.0 and 2.5 multiples of the median, respectively. No combination of dating methods results in a net decrease in detection of open spina bifida after weight adjustment.

The median maternal weights in the pregnancies affected by open spina bifida are 140 pounds for white women and 147 pounds for black women, compared with approximately 139 and 149 pounds, respectively, in over 200,000 unaffected pregnancies collected from the three centers from which the largest number of cases (79) were obtained.

Comment

Maternal weight is known to influence maternal serum AFP levels in pregnancies not affected with open spina bifida, with larger women having lower levels, on average, presumably because of dilution into a larger plasma volume. When maternal weight is not taken into account, a larger proportion of lighter women and a smaller proportion of heavier women in the unaffected population will have positive high maternal serum AFP screening results. Adjusting maternal serum AFP values for maternal weight in pregnancies unaffected with fetal open spina bifida does not change the median but does reduce variance by 0.0026.[3] Consequently, the number of false-positive screening results is reduced.

One group has reported that the detection rate of fetal open spina bifida by maternal serum AFP screening is diminished by weight adjustment, but that study included only four patients, all of whom had positive maternal serum AFP screening results before the evaluation of weight adjustment.[9] Such a reduction in screening sensitivity might be expected if the population of women with open spina bifida–affected pregnancies weighed less than the unaffected population. A 1981 British study found a slightly lower average weight among affected pregnancies,[2] whereas an American study found a slightly higher average weight[10]; in neither of these studies was the difference statistically significant. The maternal weights in pregnancies with fetal open spina bifida in this study are not different from those in women with unaffected pregnancies in the United States.

This study demonstrates a 4% increase in the detection rate of open spina bifida after weight adjustment, with a maternal serum AFP cutoff of 2.0 multiples of the median, and a 1% increase with a 2.5 maternal serum AFP cutoff of 2.5 multiples of the median when gestational age dating is based on the initial assignment method. The advantage gained from adjustment decreases at the higher cutoffs, but in no case is the open spina bifida detection rate lowered. Thus a simple calculation can result in a slight increase in the detection rate for fetal open spina bifida while simultaneously reducing the false-positive rate.

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Two-tier approach to biophysical assessment of the fetus

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The biophysical profile score is widely accepted as a superior predictor of acute-on-chronic fetal asphyxia over the nonstress test. Nevertheless, in the United Kingdom facilities for assessment of high-risk pregnancies by nonstress test are more widely available than with the biophysical profile score. After a retrospective review of 2038 biophysical assessments in 500 high-risk pregnancies, it is suggested that biophysical evaluation of the fetus can be rationalized on the basis of the clinical problem and fetal growth. Terminal acute-on-chronic fetal asphyxia can be excluded by a two-tier method of fetal assessment by initial nonstress test backed up by the biophysical profile score when the nonstress test is suboptimal. (AM J OBSTET GYNECOL 1990;163:12-7.)

Key words: Fetus, biophysical profile, nonstress test, fetal asphyxia

The majority of pregnancies are uneventful, with delivery of a normal, healthy infant. However, there are a few pregnancies in which there is a risk of chronic fetal asphyxia; examples include pregnancies with reduced fetal movements, antepartum hemorrhage, a small-for-dates fetus, and maternal hypertension.

Methods used to assess antepartum fetal well-being have changed over the past 15 to 20 years. Whereas biochemical methods were popular in the 1970s, they have now been largely replaced by biophysical methods.[1] Such biophysical tests of fetal well-being include daily fetal movement counting,[2] nonstress cardiotocography,[3] contraction stress testing (CST),[4] and biophysical profile (BPP) evaluation.[5] The nonstress test (NST) is generally accepted as a useful method of fetal assessment and is the most widely used method in the United States and United Kingdom.[3] CST, never widely used in the United Kingdom, has declined in popularity in the United States. It is generally avoided before 34 weeks if there is a history of premature labor, third-trimester bleeding, multiple pregnancy, premature rupture of the membranes, or an incompetent cervix,[6] although persistent labor has not been reported after CST.[7]

Real-time ultrasonographic scanning enables dynamic assessments to be extended further in the form of a BPP.[8-11] In a prospective clinical study of 12,620 referred high-risk pregnancies, Manning et al.[12] showed that a fetal biophysical scoring system gives an accurate method for identification of the fetus at risk of perinatal death from acute-on-chronic fetal asphyxia. The false-negative and false-positive rates are considerably lower than those reported for the NST.[4]

The biophysical profile method of fetal assessment does have disadvantages. It is time-consuming in terms of hospital personnel and equipment. Furthermore, there may be considerable inconvenience incurred by the patient having to travel long distances for frequent hospital visits.

The aim of this study was to assess whether biophysical evaluation of fetal well-being could be rationalized.

Material and methods

Bristol Feto-Maternal Assessment Unit. The Bristol Feto-Maternal Assessment Unit[5] is run by a midwife trained in obstetric ultrasonography and a specialist in fetomaternal medicine. Patients referred for fetal assessment are managed in accordance with the following protocol.

Initial visit. A detailed ultrasonographic scan for normality and size is carried out. A BPP is performed; nonstress cardiotocography is done until two episodes of fetal heart accelerations of ≥15 beats/min and ≥15 seconds occurs; subsequently the four variables—fetal breathing, tone, movement, and amniotic fluid volume—are observed by means of real-time ultrasonography. The observation period lasts until a normal score is obtained (up to 30 minutes). The scoring system described by Manning et al.[13] is used. A score of 2 is assigned when the parameter is normal and 0 when it is abnormal.

A score of 8 or 10 in 30 minutes is interpreted as normal, indicating a nonasphyxiated fetus. An equivocal test result (score = 6) is repeated within 6 hours, and if the score is the same on subsequent testing, acute-on-chronic fetal asphyxia is suspected. A score of ≤4 is considered to be strongly suspicious of acute-on-chronic fetal asphyxia. The timing and mode of deliv-

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ery are decided on the basis of fetal, obstetric, and maternal factors by the unit looking after the mother.

Subsequent visits. Biophysical profiles are carried out weekly, except in cases of severe intrauterine growth retardation, poorly controlled diabetes, or postmaturity (>42 weeks), where assessments are done twice weekly. Ultrasonographic measurements of fetal growth are repeated every 4 weeks in cases with normal growth but every 2 weeks in cases with abnormal growth. Abnormal growth is diagnosed when one or more of the following are recognized: Measurement of fetal abdominal circumference is below the 10th percentile; there is asymmetry of head and abdominal circumference values, there is decreasing fetal abdominal circumference growth trajectories crossing percentile lines.

Method. A retrospective analysis of 2038 BPPs from 500 pregnancies was undertaken. The NST for each BPP was analyzed and scored independently from the BPP as summarized in Table I. If the tracing was either of poor technical quality or abnormal with a score of ≤3, the NST was classified as "suboptimal." The evaluation was carried out by one of us (M. S. M.) without prior knowledge of infant outcome. Comparison of NST with BPP was undertaken according to fetal growth patterns, either (A) "normal growth," defined as abdominal circumference measurements following an expected growth trajectory above the 10th percentile, or (B) "abnormal growth," defined as abdominal circumference below the 10th percentile, or falling below the expected growth trajectory, or asymmetry of head and abdominal circumference values.

After the analysis of the NSTs and BPPs had been completed, the infant's outcome was recorded.

Table I. Scoring of NST

Variable	*Normal (score = 1)*	*Abnormal (score = 0)*
Baseline fetal heart rate (beats/min)	120-160	< 120, > 160
Short-term baseline varibility (beats/min)	≥ 5	< 5
Accelerations	≥ 2 Episodes of acceleration of ≥ 15 beats/min and ≥ 15 seconds' duration	< 2 Episodes of acceleration of < 15 beats/min and < 15 seconds' duration
Decelerations	Absent	Present ≥ 20 seconds and > 15 beats/min

Results

There were 514 deliveries (486 singletons and 14 twins). A total of 2038 biophysical profile scores were obtained (4.1 tests per patient; range 1 to 38). The commonest indications for referral were clinical suspicion of intrauterine growth retardation (39%), reduced fetal movements (17%), vaginal bleeding (15%) and hypertensive disease (14%). Other indications included previous stillbirth, diabetes mellitus, and multiple pregnancy. A total of 134 patients had more than one risk factor. The median gestational age at the time of referral was 34 weeks (range 24 to 44 weeks), and 62 (12%) patients were referred before 28 weeks.

The duration of real-time ultrasonographic observation was usually shorter than the maximum of 30 minutes; 1611 (79%) were completed in 10 minutes, 280 (14%) in 20 minutes, and 147 (7%) in 30 minutes.

Scores and outcomes. BPP and NST scores together with intrauterine and neonatal deaths are summarized in Table II according to fetal growth pattern. When the NST was not performed (48 cases), the gestation was often <28 weeks or the BPP score was normal ($n = 8$) without cardiotocography needed to add to the score. The majority of BPP scores were normal (98.4%). Where a test was equivocal (23 cases), it was repeated in 6 hours in 17 cases; 13 of these repeat tests were then normal. In no case did an abnormal BPP score (≤4) convert back to normal.

Relationship of NST and BPP. In 1561 cases (78.4%) there was a good correlation between the NST and BPP. A total of 423 NSTs (21.3%) were classified as suboptimal (score <4 or poor quality trace) and were followed by normal BPP scores.

In six cases the NST score was four and was associated with an equivocal BPP score of 6 (in no instance did a BPP score of ≤4 follow a NST score of 4). Among these six cases tests were repeated in five within 6 hours and BPP scores subsequently were normal (≥8). In these five cases fetal outcome was good with deliveries occurring between 1 and 6 weeks later. In the sixth case, at 40 weeks' gestation, with serial ultrasonography suggesting a symmetrically small fetus that was growing well, a BPP score of 6 was obtained after a normal NST score of 4. The BPP was repeated 1 hour later and a further score of 6 was obtained in 30 minutes. Labor was induced and a 2630 gm fetus was delivered vaginally 12 hours later. Apgar scores were 9 at 1 minute and 10 at 5 minutes.

In 26 cases the NST was suboptimal and the BPP score was equivocal or abnormal. Thirteen of these 26 cases with equivocal scores had normal scores when the assessment was repeated. Delivery was indicated in another eight cases for obstetric reasons (four cases) or because of a repeat abnormal score (four cases). The remaining five resulted in intrauterine or neonatal death and are discussed below.

Intrauterine and neonatal deaths. There were 10 intrauterine or neonatal deaths (Table III). This represents an uncorrected "reproductive loss rate" of 19.5

Table II. BPP and NST scores and baby deaths according to fetal growth pattern

Group	*Growth pattern**	*No. of mothers*	*No. of assessments*	*Optimal NST (4/4) and optimal BPP (≥8/10)*	*Suboptimal NST (<4/4) but optimal BPP (≥8/10)*	*Optimal NST (4/4) but suboptimal BPP (<8/10)*	*Suboptimal NST and BPP*	*NST not done*	*Intrauterine and infant deaths*
A	Normal	401	1330	1019	265	4	16	26	5
B	Abnormal	85	424	317	85	2	10	10	5
C	Twins	14	284	199	73	0	0	12	0
TOTAL		500	2038	1535	423	6	26	48	10

*See text.

Table III. Intrauterine and neonatal deaths (n = 10)

Case No.	*Intrauterine or neonatal death*	*Interval of assessment before death (days)*	*Gestation at delivery (wk)*	*Birth weight (gm)*	*NST score*	*BPP score and time taken*	*Indication for delivery and cause of death*	*Growth pattern (see text)*
1	Intrauterine	3	24	440	1/4	4/10, 30 min	Extreme IUGR	B
2	Intrauterine	1	25	465	Not done	6/10, 30 min	Retroplacental clot; spontaneous abortion	A
3	Intrauterine	1	25	134	1/4	2/10, 30 min	Severe IUGR; syndactyly; bilateral lung hypoplasia; bowel atresia; bilateral adrenal hypoplasia	B
4	Intrauterine	6	36	2100	1/4	6/10, 30 min	Hydropic fetus; amniocentesis showed trisomy 21; tetralogy of Fallot	A
5	Neonatal	2	38	1900	4/4	8/10, 10 min	Severe IUGR; dysmorphic fetus; chromosome abnormality (46,XX, + 22p)	B
6	Neonatal	1	33	835	2/4	8/10, 20 min	Severe IUGR; arrested growth; dysmorphic fetus; triploidy	B
7	Neonatal	3	39	4900	Not done	8/10, 10 min	Hydramnios; double-bubble and gut atresia diagnosed antenatally; inhalation of vomitus leading to respiratory failure after delivery	A
8	Neonatal	1	26	870	4/4	10/10, 5 min	Fulminating preeclampsia; cesarean section; gross prematurity	A
9	Neonatal	2	29	1520	4/4	10/10, 10 min	Premature rupture of membranes at 22 wk; premature labor and delivery; hypoplastic lungs; respiratory distress syndrome	A
10	Neonatal	1 hr	29	920	0/4	4/10, 30 min	Intrauterine growth retardation and evidence of fetal asphyxia; cesarean section; early neonatal death from gross asphyxia and prematurity; retroplacental clot	B

IUGR, Intrauterine growth retardation.

per 1000. Excluding abortuses (three cases) the gross (uncorrected) perinatal mortality rate was 13.70 per 1000 total births. The corrected perinatal mortality rate (excluding lethal abnormality and babies weighing <500 gm) of the group was 7.83 per 1000 births. There were no cases of stillbirth in a structurally normal fetus after a normal BPP score.

Abortuses. Three of the deaths occurred in utero at 24 to 25 weeks' gestation and were classified as abortions. Two of the deaths were due to asphyxia; both fetuses were growth-retarded and in addition there was placental separation in one case. The third abortus was dysmorphic.

Stillbirths. There was one intrauterine death after 26

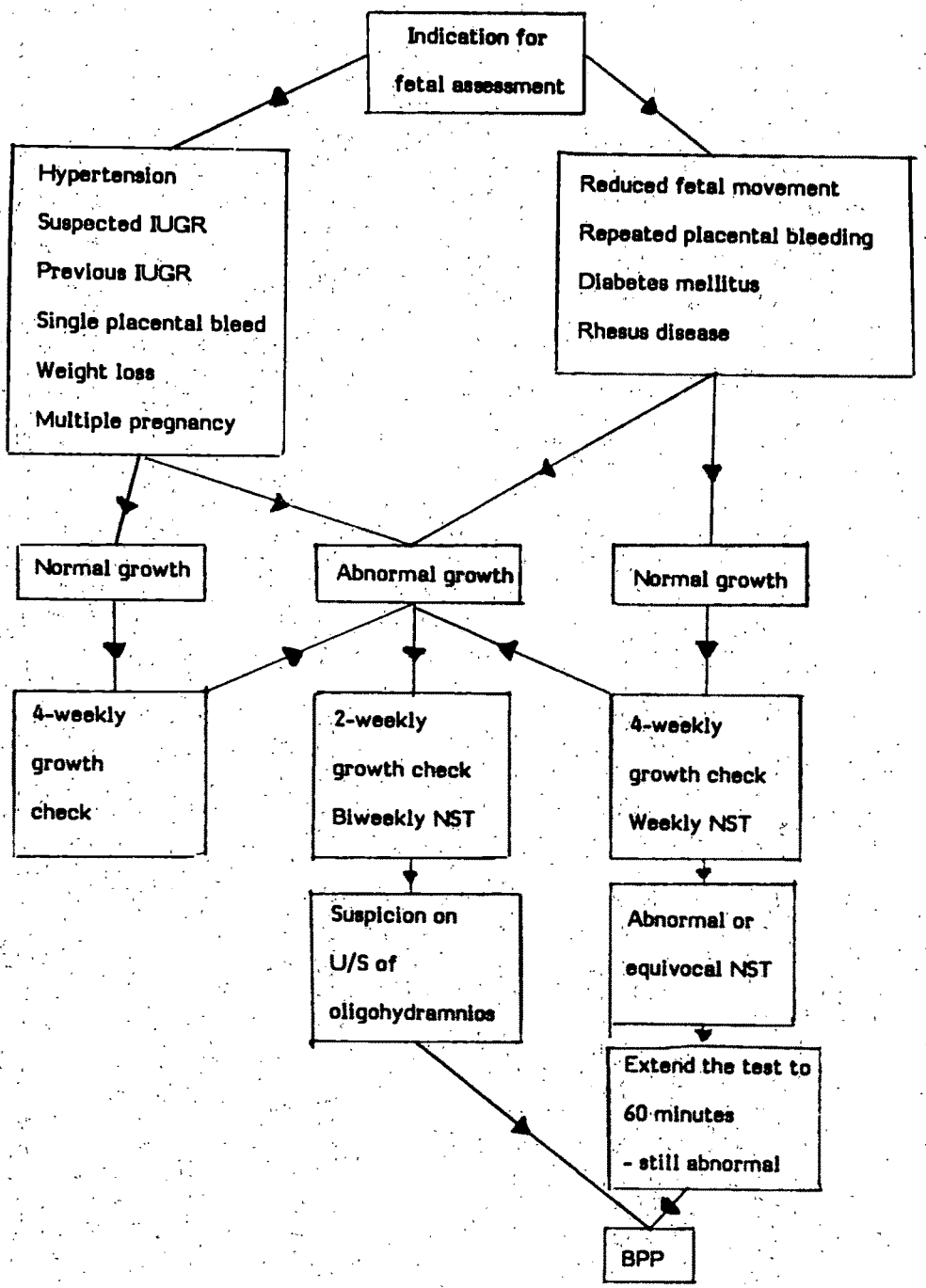


Fig. 1. Possible management protocol.

weeks, thus giving an uncorrected stillbirth rate of 1.96 per 1000 total births. This fetus was abnormal (hydrops fetalis with trisomy 21 and tetralogy of Fallot).

Neonatal deaths. There were six neonatal deaths, for an uncorrected neonatal death rate of 11.74 per 1000 births. Two infants had lethal abnormalities. Another had duodenal atresia; its postnatal management was suboptimal and it died of aspiration of vomitus. The remaining three deaths were as a result of extreme prematurity (gestations of 26 to 29 weeks). Only one had abnormal BPP and NST scores (4/10 in 30 minutes and 0/4) and was severely asphyxiated at birth.

Deaths caused by asphyxia. Three of the 10 intrauterine and neonatal deaths (two spontaneous abortions and 1 neonatal death) were due to asphyxia as outlined above. The sensitivity, specificity, and accuracy of an NST alone and a full BPP in predicting lethal fetal asphyxia are shown in Table IV.

Table IV. Accuracy of predicting lethal fetal asphyxia

	NST alone	*BPP*	
No. of tests	1990	2038	
Predicted			
Asphyxia	449	32	(9*)
No asphyxia	1541	2006	(2029*)
Developed			
Asphyxia	2†	3†	
No asphyxia	1988	2035	
Sensitivity (%)	100	100	
Specificity (%)	77.5	98.6	(99.7*)
False-positive (%)	99.6	90.6	(66.7*)
False-negative (%)	0	0	
Positive predictive power (%)	0.4	9.38	(33.3*)
Negative predictive power (%)	100	100	
Accuracy (%)	77.5	98.7	(98.7*)

*Value obtained on repeat testing where an equivocal BPP score of 6/10 was obtained.

†All predicted.

Comment

A number of biophysical tests exist that are used to assess fetal "health" or "well-being." The need for a critical view of many of these procedures has been emphasized.[14] The biophysical tests described in this paper (NST and BPP) are directed toward the detection of acute-on-chronic fetal asphyxia. Generally, they are better at confirming normality (high specificity and negative predictive power) than identifying abnormality (low sensitivity and positive predictive power). Furthermore, it is probable that the tests become abnormal relatively late in the chronic asphyxial process.

The experience of Manning et al.[12] shows that fetal biophysical scoring is an accurate method for identification of a fetus at risk of dying antepartum of asphyxia. They reported a false-negative rate of only 0.634 per 1000. This is similar to that reported for CST of 0.4 per 1000 with its potential risks and lower than that reported for the NST of 3.2 to 8 per 1000.[4, 15] Our report confirms that the BPP is superior to the NST in terms of a lower false-negative and false-positive rate. It is noteworthy that, despite theoretical limitations of the BPP from neurologic immaturity,[16] chronic fetal asphyxia was recognized with the BPP before 28 weeks in our study (Table III); this early diagnosis has been confirmed by others.[12]

However, the BPP does have the disadvantage of being a time-consuming process requiring specialist staff and frequent patient visits. Furthermore, fetal assessment with the NST is more widely available. According to our experience reported in this study, is there any way that the NST could be used safely as a first-level initial assessment in certain cases with the BPP used as a second-level subsequent assessment only in those cases where the NST is suboptimal?

In the majority of cases there was good correlation between normal NSTs and BPPs. There were no stillbirths after a NST score of 4 out of 4. In only six cases was a NST score of four out of four followed by an equivocal BPP score (6 of 10 in 30 minutes). Five of these were normal on retesting. One remained equivocal. The length of gestation was 40 weeks; labor was induced and a 2630 gm fetus was born in good condition after a 12-hour labor.

From this report we would suggest that biophysical assessment could be rationalized. After the initial biophysical assessment (including ultrasonographic screening for anomalies, fetal size, and liquor volume), further assessment of ultrasonographically normal fetuses could be determined on the basis of the clinical problem and whether the subsequent growth is normal (see Fig. 1). Where the clinical problem carries a risk of abnormal fetal growth (for example, hypertension, possible intrauterine growth retardation, weight loss, or multiple pregnancy), provided the growth (assessed every 4 weeks) is normal, then no further biophysical assessment is necessary. If the growth is abnormal, increasing the likelihood of acute-on-chronic asphyxia,[14] then biweekly NSTs and growth checks every 2 weeks should be undertaken. Where the clinical problem carries not only a risk of abnormal fetal growth but also of acute compromise without abnormal growth (for example, recurrent placental bleeding, reduced fetal movement, diabetes mellitus, or rhesus isoimmunization) then, in addition to growth checks, the NST also must be undertaken. This can be weekly if growth is normal and biweekly if abnormal. The BPP can be reserved for those cases where the NST is abnormal or equivocal or where there is a suspicion of oligohydramnios on ultrasonogram.

Using this approach we could reduce the workload of NSTs by >60% and BPPs by >75%. This latter figure could be improved further if the period of testing with equivocal NSTs was extended to 60 minutes since many suboptimal NST results in 30 minutes are merely a reflection of the periodic nature of fetal behavior. An antepartum NST is far more widely available than biophysical scoring; furthermore, fetal heart rate monitoring could be undertaken by the mother herself using the telephone[17, 18] and could reduce the demands on hospital and community staff even more.

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Sinusoidal fetal heart rate pattern during cardiopulmonary bypass

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A gravida 3, para 2 woman underwent an emergency mitral valve replacement at 24 weeks' gestation. A sinusoidal fetal heart pattern was recorded throughout cardiopulmonary bypass. This pattern persisted despite a pump flow maintained at 31 ml/m^2 min and an intravenous infusion of phenylephrine to maintain the mean systemic arterial pressure at 50 mm Hg. (AM J OBSTET GYNECOL 1990;163:17-8.)

Key words: Fetal heart rate, cardiopulmonary bypass, pregnancy, general anesthesia

Infective endocarditis associated with congestive heart failure and systemic embolization has a grave prognosis that may be modified only by a valve replacement. This situation is rare in pregnancy. Emergency open heart surgery during pregnancy may not carry a higher risk for the patient, but the risk to the fetus is great. With advances in the management of these cases, particularly with fetal monitoring, the fetal mortality rate may be as low as 9.5%, as shown in a recent report.[1]

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We monitored a patient who underwent emergency mitral valve replacement at 24 weeks' gestation because of infective endocarditis. We recorded a sinusoidal pattern during the cardiopulmonary bypass. This type of fetal heart rate pattern has not previously been reported in association with surgery during pregnancy.

Case report

A 32-year old woman, gravida 3, para 2, was admitted to our hospital at 24 weeks' gestation because of *Streptococcus viridans* endocarditis that had resulted in mitral regurgitation with congestive heart failure refractory to medical treatment. She had a right cerebrovascular accident before her transfer to our institution. Medical history was significant for a dental procedure approximately 6 weeks before this admission. No antibiotic

prophylaxis was used since she was not known to have mitral valve prolapse. Despite intensive medical management, the congestive heart failure worsened and replacement of the mitral valve was recommended. After insertion of a pulmonary artery catheter and with left uterine displacement, external fetal heart rate monitoring with a model 8030A Hewlett-Packard cardiotocograph was begun. The initial recording showed a normal fetal heart rate with good variability. After induction of anesthesia with intravenous diazepam and sufentanil, a gradual loss of beat-to-beat variability of the fetal heart rate was observed. After the initiation of cardiopulmonary bypass, a persistent sinusoidal pattern with a rate of 120 to 150 beats/min was observed. Although the pump flow was maintained at 31 ml/m²/min, mean arterial pressure was 25 to 30 mm Hg. Phenylephrine, an α-adrenergic receptor agonist, was infused intravenously to raise the mean arterial pressure to 50 mm Hg. It did not alter the existing sinusoidal fetal heart rate pattern. Rectal temperature was maintained at 37° C. On completion of the valve replacement, the patient was weaned from cardiopulmonary bypass. Intravenous infusions of dopamine and isoproterenol were required to maintain a cardiac index of 31/m²/min. The fetal heart rate returned to the prebypass pattern with a continued decreased beat-to-beat variability. Normal variability did not return until several hours after operation. The patient was monitored with serial ultrasonography. Biophysical profile measurements were started at 28 weeks' gestation and increased to twice weekly at 34 weeks' gestation. At 39 weeks' gestation labor was induced because of poor fundal growth and suspected intrauterine growth retardation. A healthy female infant weighing 2885 gm was delivered with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. A postpartum tubal ligation was performed. The child has been followed up for 2 years and her developmental status is normal.

Comment

The fetal hazards during open heart surgery appear multiple but their precise mechanisms are undetermined. Fetal distress may occur because of low uterine blood flow, uterine artery spasm, particulate or bubble emboli, and sludging of blood, which may interfere with placental circulation.

Persistent fetal bradycardia and fetal bradycardia with late deceleration patterns have been reported during cardiopulmonary bypass.[2] Temporary improvement may occur with an increase of flow rate; however, fetal heart rate usually deteriorates again to persistent bradycardia with prolonged bypass.

In our patient a persistent sinusoidal fetal heart rate pattern was recorded. It may have reflected fetal acidosis, despite a perfusion flow rate of 31 ml/m²/min. Since uterine perfusion is dependent on perfusion pressure, mean arterial pressures of 70 mm Hg have been recommended. An α-adrenergic receptor agonist, phenylephrine, was infused with no changes in the fetal heart rate pattern. One might therefore conclude that the perfusion flow rate is more important than perfusion pressure for maintaining uterine blood flow during cardiopulmonary bypass.

In summary, a persistent sinusoidal heart rate pattern was recorded during a normothermic, high-flow, cardiopulmonary bypass. Increasing the systemic vascular resistance with an α-adrenergic receptor agonist did not restore the fetal heart rate to the prebypass pattern. More studies and experience are needed to learn the effect of nonpulsatile cardiopulmonary bypass on uterine and umbilical circulations.

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Risk factors for perinatal group B streptococcal disease after amniotic fluid colonization

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A group of 1031 parturient women at high risk for intraamniotic infection were studied. Women in whom group B streptococci grew from cultures of the amniotic fluid did not differ in clinical risk factors when compared with similar parturient women without group B streptococcal colonization of amniotic fluid. Patients who had perinatal group B streptococcal disease (maternal or neonatal bacteremia) did not differ from those without disease, by maternal or neonatal acute antibody levels or antibody response, inoculum size, or serotype of the colonizing strain. (AM J OBSTET GYNECOL 1990;163:19-25.)

Key words: Group B streptococci, intraamniotic colonization

Many studies have assessed risk factors for perinatal group B streptococcal disease, yet our understanding is incomplete. The goal of this investigation was to assess clinical and selected laboratory risk factors for group B streptococcal maternal infection and early-onset neonatal sepsis in a well-defined, high-risk population. Because most early-onset neonatal infections begin in utero, we were especially interested in determining the role of amniotic fluid colonization, amniotic fluid inoculum size, maternal antibody level, maternal antibody response, and maternal clinical characteristics that might help predict the risk for perinatal disease.

Methods

Patient population. Patients were predominantly indigent and of Mexican-American extraction, delivered at Medical Center Hospital, San Antonio, Texas, between July 1979 and December 1987. Patients selected for study included parturient women with clinically diagnosed intraamniotic infection and asymptomatic women with duration of ruptured membranes >10 hours.

Clinical data. Data were collected prospectively from maternal and neonatal hospital charts and included 25 clinical risk factors or outcome variables. Patients were divided into four categories, according to the clinical diagnosis. (1) There were 467 patients with intraamniotic infection defined on the basis of an oral temperature >37.8° C plus two or more of the following: maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), uterine tenderness, foul odor of the amniotic fluid, or peripheral leukocytosis (>12,000/mm³). (2) There were 99 patients with endometritis, defined as a postpartum oral temperature >37.8° C with localized uterine tenderness. (3) There were 124 patients with fever only, defined as a transient temperature elevation to >37.8° C without localizing signs and not receiving therapeutic or prophylactic antibiotics. (4) There were 341 asymptomatic parturient women with temperature <37.8° C, who had rupture of membranes >10 hours and received no therapeutic antibiotics. Maternal sepsis was diagnosed on the basis of clinical suspicion and confirmed by a positive blood culture. Neonatal sepsis was suspected in infants whose mothers had a clinical diagnosis of intraamniotic infection, in preterm infants with rupture of membranes >24 hours, or in infants with clinical signs of sepsis. Neonatal sepsis was confirmed by isolation of a pathogenic organism from the blood. Neonatal pneumonia was defined as respiratory symptoms with a patchy infiltrate on chest x-ray film. Therapeutic antibiotics were used in cases of suspected sepsis pending culture results but were discontinued if sepsis was not confirmed. Infants were treated according to clinical indications and not solely on the basis of an amniotic fluid culture that was positive for group B streptococci.

Microbiologic data. Patients were further classified by the presence or absence of group B streptococci in amniotic fluid. Amniotic fluid was obtained from all patients by aspiration of an intrauterine pressure catheter that had been inserted for obstetric indications. In

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Table I. Maternal clinical diagnosis by amniotic fluid group B streptococcal culture status

Maternal clinical diagnosis	*n*	*Culture for group B streptococci*	
		Positive	*Negative*
Intraamniotic infection	467	75 (56%)*	392 (44%)*
Endometritis	99	14 (11%)	85 (9%)
Fever only	124	9 (7%)	115 (13%)
Asymptomatic	341	35 (26%)	306 (34%)
TOTAL	1031	133	898

*$p < 0.05$, χ^2 goodness-of-fit test for positive group B streptococci versus negative group B streptococci in diagnostic category.

Table II. Neonatal diagnosis by amniotic fluid group B streptococcal culture status

Neonatal diagnosis	*n*	*Culture for group B streptococci*	
		Positive	*Negative*
Normal	479	46 (35%)*	433 (49%)*
Sepsis confirmed	26	12 (9%)*†	14 (2%)*
Sepsis suspected	479	67 (51%)*	412 (46%)*
Pneumonia	27	5 (4%)	22 (2%)
Other infections	13	2 (2%)	11 (1%)
TOTAL	1024	132	892

*$p < 0.05$, χ^2 goodness-of-fit test for positive group B streptococci versus negative group B streptococci in diagnostic category.

†Group B streptococci, 7 cases; *Escherichia coli*, 2 cases; α-hemolytic streptococci, *Haemophilus influenzae*, *Streptococcus viridans*, 1 case each.

those patients with a clinical diagnosis of intraamniotic infection, the specimen was collected before the administration of antibiotics. To minimize the possibility of contamination, the first 7 ml (equivalent to the volume of the catheter) was discarded, and the next 5 to 20 ml was collected in a separate plastic syringe. Collection of vaginal swabs during labor began in March 1986. Collection of neonatal surface cultures began in January 1986. Neonatal cultures were obtained from the external auditory canal and throat, in the delivery room when possible but always within 24 hours of birth. All amniotic fluid specimens were transported to the laboratory and plated quantitatively within 60 minutes. All specimens were plated on a variety of media for aerobes and anaerobes.[1] Beginning in January 1986, specimens were also cultured in selective media for group B streptococci consisting of Todd-Hewitt broth with 8 mg/L gentamicin and 15 mg/L nalidixic acid. Maternal and neonatal blood cultures were obtained when clinically indicated with the use of two 100 ml bottles containing trypticase soy broth with 3% carbon dioxide and 0.03% sodium polyanethol sulfate (BBL, Cockeysville, Md.). Isolates were identified by standard techniques. Group B streptococci isolates were serotyped by previously reported methods.[2]

Serologic data. Maternal and neonatal blood was collected within 48 hours of delivery and at 4 to 6 weeks post partum from available patients. Sera were stored at −70° C until assayed. Quantitative determinations for total antibody specific for the polysaccharide antigens of group B streptococcal types Ia, Ib, II, and III were performed by an enzyme-linked immunosorbent assay[3] adapted for use with plastic microwells.[4] A peroxidase-labeled antihuman immunoglobulin second antibody was used that detected antibodies of all classes. Results were expressed as micrograms of antibody protein per milliliter.[3, 4] Serologic response in paired sera was assessed by the mean difference of antibody levels in sera from convalescent and acute conditions. Amniotic fluid antibody levels were determined[4] in a small group of patients.

Statistical methods. Discrete clinical data were analyzed across all diagnostic categories and within each by χ^2 goodness of fit test or by Fisher's exact test, where appropriate. Continuous data were analyzed (1) within each diagnostic category by two-tailed Student's *t* test, (2) across all diagnostic categories by two-way analysis of variance with the presence or absence of group B streptococci and diagnoses as the main effects, and (3) within each group B streptococcal culture status group by the Student–Newman-Keuls procedure. Serologic data were analyzed by two-tailed Student's *t* test.

Results

Clinical risk factors. A total of 1031 patients were enrolled in the study. One hundred thirty-three (12.9%) patients had positive cultures for group B streptococci in the amniotic fluid (group 1). The remaining 898 patients formed group 2. The clinical diagnoses by amniotic fluid group B streptococcal culture status are shown in Table I. When group B streptococci were present in the amniotic fluid, significant clinical risk factors by analysis of covariance included a longer duration of internal monitoring (12.9 ± 7.0 vs 10.9 ± 6.1 hours, $p = 0.003$) and a slightly, but significantly higher temperature post partum (37.9° ± 0.7° C vs 37.2° ± 0.7° C, $p = 0.028$). All other clinical risk factors and variables, including duration of labor, maximum temperature in labor, and number of vaginal examinations, were indistinguishable by amniotic fluid group B streptococcal culture status.

Neonatal diagnoses by amniotic fluid group B streptococcal culture status are shown in Table II. The rate of culture-confirmed neonatal group B streptococcal sepsis in infants of mothers with group B streptococci

Table III. Maternal acute type-specific homologous antibody levels compared with nonhomologous antibody levels

	*Homologous**		*Nonhomologous†*	
Infecting serotype	*n‡*	*Antibody level (μg/ml)*	*n‡*	*Antibody level (μg/ml)*
Ia	7	24.8 ± 28.4	23	21.7 ± 15.3
Ib	10	22.0 ± 11.7	20	21.8 ± 17.7
II	5	44.7 ± 41.3	25	52.0 ± 44
III	7	25.8 ± 14.7	23	31.7 ± 18.7

Antibody levels are expressed as mean ± SD.

**Homologous,* Antibody to serotype isolated from individual's amniotic fluid.

†*Nonhomologous,* Antibody to remaining three serotypes not isolated from individual's amniotic fluid.

‡Sum of homologous plus nonhomologous antibody measurements equals 30.

Table IV. Maternal antibody change, type-specific homologous versus nonhomologous

	Homologous		*Nonhomologous*	
Serotype	*n**	*Change in antibody level† (μg/ml)*	*n**	*Change in antibody level† (μg/ml)*
Ia	5	17.9 ± 24.3	23	2.8 ± 14.6
Ib	10	18.4 ± 40.2	18	3.1 ± 9.3
II	5	6.1 ± 27.6	23	14.0 ± 34.7
III	7	5.8 ± 15.0	21	13.3 ± 30.5

Antibody levels are expressed as mean ± SD.

*Sum of homologous plus nonhomologous antibody change measurements equals 28.

†Convalescent level minus acute level.

from cultures of the amniotic fluid was 7 of 133 (5.3%). We compared clinical risk factors of group I mothers whose babies had group B streptococcal sepsis with those of mothers whose infants did not. There was a significantly higher maximum postpartum temperature in the mothers of septic infants (38.5° ± 1.0° C vs 37.9° ± 0.7° C, $p = 0.045$) but no other significant differences in clinical risk factors.

Transmission of group B streptococci. Group B streptococci were identified in 20% (42/212) of vaginal cultures. When group B streptococci were detected in the vagina, they were also cultured from the amniotic fluid in 81% (34/42). There were no differences in the clinical factors between those patients without transmission of group B streptococci from the vagina to the amniotic fluid and the 34 patients with transmission. In 12% of cases (4/34), group B streptococci were recovered from amniotic fluid but not from the vagina. When group B streptococci were cultured from the amniotic fluid, 76% (22/29) of the corresponding neonates with cultures for group B streptococci were colonized. There was no difference in the rate of neonatal colonization whether the mother did or did not receive therapeutic antibiotics (usually penicillin or ampicillin plus gentamicin) before delivery (4/6 or 67% vs 16/21 or 76%, $p = 0.5$).

Serologic results. Paired sera from acute and convalescent conditions were available from 28 mothers and 13 babies who had group B streptococci recovered from the amniotic fluid. Acute sera only were available from an additional two mothers and three babies. The isolate from one patient could not be typed. Seven mothers were colonized with Ia (23%), 10 with Ib (33%), five with II (17%), and seven with III (23%). Antibodies to all four serotypes were assessed in each subject. To evaluate the specific serologic response, we compared the individual's antibody response to the serotype that was isolated from the amniotic fluid (homologous) with the antibody response to the three serotypes that were not isolated (nonhomologous) as a background control. Mean maternal acute type-specific homologous antibody levels are compared with mean nonhomologous antibody levels in Table III. There were no significant differences in antibody levels. Table IV compares the antibody response, as assessed by mean convalescent minus mean acute antibody levels for type-specific homologous and nonhomologous serotypes. There were no significant differences. Mean maternal acute type-

Table V. Maternal acute type-specific homologous antibody levels (all isotypes) in cases of maternal or neonatal bacteremia versus those without bacteremia

	Bacteremia		*No bacteremia*	
Serotype	*n**	*Antibody level (μg/ml)*	*n**	*Antibody level (μg/ml)*
Ia	1	80.6 ± 55.5	6	15.5 ± 15.5
Ib	3	20.3 ± 4.1	7	22.7 ± 14
II	2	18.4 ± 10.7	3	62.3 ± 46.9
III	3	34.3 ± 14.3	4	19.4 ± 13.1

Antibody levels expressed as mean ± SD.
*Sum of bacteremic plus nonbacteremic cases equals number of patients infected with each serotype.

Table VI. Maternal antibody change in maternal or neonatal bacteremia

	Bacteremia		*No bacteremia*	
Serotype	*n*	*Change in antibody level (μg/ml)*	*n*	*Change in antibody level (μg/ml)*
Ia	1	49.2	4	10.0 ± 19.4
Ib	3	47.6 ± 62.2	7	5.9 ± 22.8
II	2	−0.3 ± 0.3	3	10.3 ± 38.2
III	2	21.8 ± 13.2	5	−0.6 ± 10.9

Antibody levels expressed as mean ± SD.

specific homologous antibody levels in patients with either maternal or neonatal bacteremias (five maternal and four neonatal) are shown in Table V. The distribution of serotypes in cases of bacteremia is similar to that of cases without bacteremia. Maternal antibody response in patients with either maternal or neonatal bacteremias is shown in Table VI. There are no significantly different results by this analysis, although numbers are small and the standard deviations are large.

Neonatal acute antibody levels varied from 4% to 46% of maternal levels for type-specific antibody and 3% to 19% of maternal levels for nonhomologous antibody. The mean changes in type-specific homologous and nonhomologous antibodies in neonates are shown in Table VII. The rise in type Ia homologous antibody is significantly higher than the rise in nonhomologous type Ia antibody. In all cases serotypes of the group B streptococcal isolates from the neonates were concordant with the isolates from their mothers.

Antibody levels were assayed in 50 amniotic fluid specimens. Mean levels in amniotic fluid were 0.04 ± 0.10 μg/ml for type Ia, 0.20 ± 0.13 μg/ml for type Ib, 0.05 ± 0.05 μg/ml for type II, and 0.14 ± 0.13 μg/ml for type III. These levels were 2% to 4% of those in paired acute maternal sera. For paired amniotic fluid and serum, the Pearson correlation coefficient was low, indicating no linear relationship. Similarly, there were no apparent nonlinear relationships.

Inoculum size. There was no significant relationship between quantitative amniotic group B streptococcal cultures and neonatal outcome. For example, 10 of 12 (83%) mothers of babies with group B streptococcal sepsis or pneumonia had group B streptococcal colony counts of >100,000/ml versus 86 of 120 (72%) well babies.

Comment

Several strategies to reduce the risk of early neonatal group B streptococcal sepsis have been attempted with variable success. Attempts to eliminate the carrier state in antepartum patients have uniformly failed,[5-7] probably because antibiotics only suppress the bacteria and mothers may become recolonized from the lower gastrointestinal tract or by sexual transmission.[8] Neonatal penicillin prophylaxis also has proved unsuccessful, as most neonates with early-onset sepsis already have bacteremia at birth.[9, 10] The most successful approach has been selective intrapartum therapy of group B streptococcal carriers with known risk factors for neonatal group B streptococcal sepsis (prematurity, prolonged duration of membrane rupture, and intrapartum fever).[11-14] One difficulty with this approach is that, in patients whose sole risk factor is fever in labor, therapy may begin too late to prevent disease. Boyer and Gotoff[13] found that with intrapartum therapy there were no cases of neonatal sepsis in patients at risk. However, in six of 23 patients with fever as the

Table VII. Neonatal change in antibody to type-specific group B streptococci

	Homologous		*Nonhomologous*	
Serotype	*n*	*Change in antibody level* (μg/ml)*	*n*	*Change in antibody level* (μg/ml)*
Ia	2	63 ± 9.3†	11	0.6 ± 1.3
Ib	5	−1.8 ± 2.9	8	−0.3 ± 0.8
II	2	−4.9 ± 14.2	11	1.9 ± 12.8
III	3	0	10	−2.7 ± 4.0

Antibody level expressed as mean ± SD.
*Convalescent minus acute antibody level.
†$p < 0.05$, two-tailed Student's t test.

sole risk factor, the infants were still colonized with group B streptococci.[14] This is in agreement with our finding that intrapartum therapy after intraamniotic infection was clinically evident did not decrease the rate of vertical transmission of group B streptococci to the neonate from the amniotic fluid. Another drawback of the approach by Boyer and Gotoff is it requires antepartum screening for group B streptococcal carriers. This poses a major logistic problem for many obstetric services, especially where a large population of patients may have late prenatal care or none. Rapid diagnostic tests have not been demonstrated to be sensitive or specific enough to be clinically useful.[15]

A major difficulty in designing an effective prophylaxis protocol has been incomplete understanding of the pathophysiologic features of group B streptococcal perinatal disease. There are at least three basic mechanisms by which a colonizing organism can become a disease-producing organism: an overwhelming inoculum, a compromised host, or a highly virulent strain. Most studies have examined a hypothesis concerning one of the potential mechanisms. We felt that by examining multiple potential mechanisms in a group of well-defined patients with known risk factors we could relate the roles of the selected variables. Since colonization of the uterine cavity is presumably the first step to invasive perinatal disease, the ideal group for comparison would be patients with vaginal group B streptococcal colonization without amniotic fluid colonization. However, there were only eight patients in this group. We therefore compared patients with and without group B streptococci in the amniotic fluid.

We examined the role of the inoculum by several approaches. We quantitated the inoculum in amniotic fluid and found we could not differentiate infants with sepsis from well infants by the colony count of group B streptococci in the amniotic fluid. The first step in development of invasive disease is colonization. We found that group B streptococci were transmitted vertically to the fetus in 76% of cases when the organism was present in the amniotic fluid. In eight reports where transmission from a colonized vagina to the neonate was examined, the mean transmission rate was 46% with a range of 34% to 72%.[10, 13, 16-21] Our patients were selected by the presence of membrane rupture >10 hours or intraamniotic infection. Therefore it is possible that all of our patients had unusually large lower genital tract colony counts and that the mere presence of group B streptococci in the amniotic fluid implies a large vaginal inoculum. In fact, in our patients 89% of group B streptococcal vaginal carriers had group B streptococci in the amniotic fluid while in labor. It is not possible to determine whether this is a usual occurrence or simply related to the method of patient selection. Boyer reported a group B streptococcal neonatal sepsis rate of 0.6 in 100 term patients with vaginal colonization[12] in contrast to our rate of 5 of 100 term patients with amniotic fluid colonization. Another factor reported to increase the risk of neonatal sepsis is prolonged duration of membrane rupture, which presumably increases inoculum size in amniotic fluid. In Boyer's studies a duration of membrane rupture of >18 hours increased the risk sevenfold.[11] Although the duration of membrane rupture does not distinguish the neonatal sepsis cases in our study, the long mean duration of rupture of membranes may explain the excess of cases of neonatal sepsis compared with those in previously reported series.

Anthony et al.[22] noted that 36% of women are chronic carriers of group B streptococci and that on serial culturing the vaginal cultures will consistently be positive for group B streptococci. Twenty percent of women will be transient carriers with only one positive culture, followed and preceded by negative cultures, while another 15% will be intermediate carriers, with several transient episodes. The remaining 29% of patients did not fit into any of these categories. Others[23] have noted that mothers delivered of infants with group B streptococcal sepsis are chronic carriers of group B streptococci. This suggests a host deficiency, and there has been much interest in whether these mothers can be distinguished by a lack of protective antibody level or

a deficient antibody response. A level of 2 μg/ml[24] of immunoglobulin G has been used to designate "protective" antibody status. Because absolute antibody levels are not well standardized from one laboratory to another, we chose not to define an arbitrary level of protective antibody but to compare acute antibody levels between clinically defined groups of patients.

Previous investigators have reported a lower acute antibody level in mothers with sepsis or mothers of infants with sepsis compared with asymptomatic colonized mothers with asymptomatic infants.[25-27] We could not confirm these findings. In addition, mothers of septic infants have been reported to be poor antibody responders when compared with mothers of well infants.[25, 26, 28] Our results show that the acute antibody levels are not significantly different and antibody response in mothers with bacteremia is not significantly different from that of women without bacteremia. Mean acute homologous antibody levels were higher in types Ia and III but lower in types Ib and II. We suspect there is no real difference. We note that the mean change in homologous antibody was substantially greater for serotypes Ia, Ib, and III. Because of the small sample size, there may have been real, but undetected, larger rises in antibody in cases of bacteremia.

Prematurity is a major risk factor for group B streptococcal sepsis. It has been postulated that these infants are more vulnerable because of relative lack of passive protection from transplacental immunoglobulin G when they are born before 32 weeks. In our study six of seven infants with group B streptococcal sepsis were term infants, but so were infants of approximately 90% of the pregnancies studied. Acute antibody levels in the seven mothers delivered of these infants were comparable to those of the other mothers. Unfortunately, because serologic data were available in only one infant, we cannot comment on the role of passive antibody transfer.

The third factor potentially leading to the development of invasive disease is that of strain virulence. It has been suggested that serotype III is the most virulent, causing >90% of late-onset neonatal disease and up to 80% of early-onset disease.[9, 29] In contrast, in 14 studies type III represents ony a mean of 40% of serotypes in asymptomatic vaginally colonized women.[5-9, 12, 17-19, 21, 30-33] The distribution of serotypes in our patients is consistent with that reported in the latter studies. It therefore does not appear that some serotypes are more likely to ascend to the uterine cavity from the vagina during labor.

In this group of high-risk patients, we were unable to distinguish mothers delivered of infants with sepsis by inoculum size, serum or amniotic fluid antibody status, or serotype. The rate of neonatal group B streptococcal sepsis is unusually high in this group of patients. It is possible that by selecting a group with prolonged membrane rupture or clinically evident intraamniotic infection we are obscuring the role of inoculum size. The role of protective maternal antibody appears to be minimal. The commonly used method of characterizing strain virulence by serotype is probably an oversimplification. The role of strain virulence deserves more investigation.

The current strategy is intrapartum therapy of patients at high risk because of prolonged membrane rupture or fever. Our study suggests this may be too late for a significant number of patients. Until we have a better understanding of the mechanism of transition from asymptomatic colonization to infection with group B streptococci, our attempts at prophylaxis are hampered.

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Blood flow velocity and pulsatile diameter changes in the fetal descending aorta: A longitudinal study

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Blood flow velocity and pulsatile diameter changes in the fetal descending aorta were measured subsequently with pulsed Doppler ultrasonography and phase-locked echo-tracking technique, respectively. Blood flow velocity and pulse-wave curves wih equal beat-to-beat intervals were synchronized by external fetal electrocardiogram. The systolic increase in blood flow velocity and in vessel diameter started simultaneously. The velocity peak preceded the diameter peak by a significant margin (p in the range 0.0001 to 0.0014). The time interval was more pronounced in the thoracic than in the abdominal part of the aorta and was slightly smaller near term. The effective diameter, calculated from the synchronized integrals of the blood flow velocity and the diameter curves, was significantly greater (p in the range 0.0001 to 0.0016) than the mean diameter. The difference tended to decrease with advancing gestational age and was more pronounced in the thoracic than in the abdominal aorta. The maximum error incurred by the use of nonsimultaneous measurements of blood flow velocity and vessel diameter when calculating volume blood flow was found to be <8% and thus probably of little practical importance. (Am J Obstet Gynecol 1990;163:26-9.)

Key words: Aortic diameter, blood flow, fetal, ultrasonography

The noninvasive method to measure blood flow velocity in the fetal aorta by application of combined real-time and pulsed Doppler ultrasonographic techniques[1] has become an important contribution to the surveillance of fetal circulation in utero. However, the estimation of volume blood flow, calculated from the time-averaged mean blood flow velocity and the vessel diameter, is not particularly accurate.[2, 3] One of the main sources of error is the impossibility of simultaneous measurement of the blood flow velocity and the diameter of the vessel because of ultrasonographic interference. Usually the mean of 10 static measurements of the diameter from real-time images has been taken as a value representative for the average caliber and included in the calculation of volume blood flow.[4] Furthermore, the time lag between the pulsatile courses of velocity and pressure[5] and that of the diameter has not been taken into consideration. The possible influence of these factors on the calculation of volume blood flow in the thoracic aorta of term fetuses has been presented and discussed in earlier studies that used fetal electrocardiogram (ECG) for the synchronization of the mean blood flow velocity and diameter curves.[6, 7] To investigate these questions further and to analyze the possible effects of gestational age, a longitudinal study was performed with measurements at two different sites on the fetal descending aorta.

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Material and methods

To measure the fetal aortic blood flow velocity a combination of a 2 MHz pulsed Doppler instrument (Alfred, Vingmed, Horten, Norway) and a 3 MHz real-time linear array scanner (ADR, Tempe, Ariz.) were used.[2] The fetal aorta was localized in a longitudinal section with the real-time transducer held parallel to the vessel. The Doppler transducer was attached to the real-time transducer at a fixed angle of 45°, thereby enabling correction of the measured blood flow velocity for the angle. The Doppler shift signals were analyzed on-line by a spectrum analyzer (Daisy, Vingmed, Horten, Norway). Maximum and mean blood flow velocity were estimated automatically on-line and the analog signals of the mean velocity were stored on magnetic tape simultaneously with the fetal ECG signals and were played back later on a chart recorder.

The pulsatile changes in the fetal aortic diameter were recorded with an electronic phase-locked echo-tracking instrument (Diamove, Teltec, Lund, Sweden) built into the real-time ultrasonography scanner.[8] The spatial resolution of the system was 14 μm at 1.28 kHz repetition frequency. The electronic markers of the tracking gate were locked to the inner surface of the opposite vessel walls in the longitudinally visualized fetal aorta, the diameter thereby was measured continuously in a plane perpendicular to the longitudinal axis

of the vessel. The analog output signals were stored on magnetic tape simultaneously with the fetal ECG signals and then were played back later on a chart recorder.

The blood flow velocity and the aortic diameter were measured subsequently with as short a time interval as possible. A switch was used to alternate between the Doppler instrument and the real-time scanner. All recordings were performed during periods of fetal quiescence without breathing or gross movements.

External fetal ECG was obtained with a custom-made electrocardiograph,[9] producing signals sufficient to define fetal QRS complexes. These complexes were used to select equal beat-to-beat intervals (maximum interbeat difference permitted, <5%). This was essential for the synchronization of individual mean blood flow velocity and aortic diameter curves of similar pulse duration. For each fetal measurement, velocity and diameter curves from 10 equal cardiac cycles were fed into a microcomputer with a digitizer (HIPAD, Houston Instruments, Houston, Tex.). The calculations were performed by integrating 50 sections per cycle of the synchronized blood flow velocity and aortic diameter traces. The aortic stroke volume was calculated by the equation[6]:

$$Q = \frac{\int_t V \cdot d^2 \cdot \pi}{4 \cdot \cos 45°}$$

where t = pulse duration, Q = stroke volume, V = mean blood flow velocity, and d = vessel diameter.

The aortic stroke volume was also correlated to the fetal weight estimated from the ultrasonographically measured fetal head and abdominal diameters.[10] From the values of the volume blood flow (Q′) in ml/min (Q′ = Q · FHR) (where FHR = fetal heart rate) and the mean blood flow velocity (V), an effective diameter (Deff) was obtained according to the equation[6]:

$$\text{Deff} = \sqrt{\frac{4 \cdot Q'}{V \cdot \pi \cdot 60}}$$

Deff was then compared with the mean aortic diameter measured with the echo tracker. To be able to study the time intervals between the velocity and the diameter curves, the velocity signals were corrected for the delay of 20 milliseconds caused by the mean velocity estimator.

Statistics were on the basis of the Student *t* test for paired observations and the Mann-Whitney rank sum test for unpaired observations.

Twelve healthy women with uncomplicated singleton pregnancies participated in the study after they gave their informed consent. Three longitudinal measurements were performed on the descending aorta of each fetus (at gestational ages 28 to 29, 33 to 34, and 38 to 39 completed weeks). Gestational age had been ascertained in all fetuses by ultrasonographic fetometry in early pregnancy.

The ultrasonographic measurements of the blood flow velocity and the diameter were obtained in each fetus just above the level of the fetal diaphragm and that of the aortic bifurcation. Some measurements were not applicable either because of difficulty in identification of the recorded fetal QRS complexes or because of nonconcurrent cycles in the blood flow velocity and the diameter curves.

Results

Table I shows the mean values (±SD) of FHR, mean blood flow velocity, aortic stroke volume, weight-related aortic stroke volume, the effective diameter, and the mean diameter on the basis of the number of accepted recordings at the thoracic and abdominal levels of the descending aorta in the three gestational periods.

Neither the FHR nor the mean blood flow velocity changed significantly with gestational age. The aortic stroke volume, when correlated to estimated fetal weight, varied slightly in the thoracic aorta but showed a tendency in the abdominal aorta to decrease with advancing gestational age.

The mean and the effective diameter both increased linearly with gestational age. The effective diameter was significantly greater (p in the range 0.0001 to 0.0016) than the mean diameter at both levels of the aorta in all three gestational periods. The relative difference, expressed in percentage of the mean diameter, showed a decreasing tendency with advancing gestational age at both levels of the aorta. The relative difference was more pronounced in the thoracic than in the abdominal part of the vessel.

Table II shows the mean values (±SD) for the time interval between the first peak of the QRS complex and the onset of the velocity and of the diameter curves, respectively, and for the time interval between the first peak of the QRS complex and the maximum of the velocity and of the diameter curves, respectively.

The onset of the systolic increase in velocity slightly preceded that of the diameter, except in late pregnancy, at the thoracic level of the aorta. The systolic velocity peak significantly preceded (p in the range 0.0001 to 0.0014) the systolic diameter peak. The relative time difference, expressed in percentage of the time interval between the first peak of the QRS complex and the velocity peak, was more pronounced in the thoracic than in the abdominal part of the fetal aorta, irrespective of gestational age. A slightly smaller relative difference at both levels of the vessel was also seen near term.

Neither the diameter difference (Deff − Dmean)

Table I. Mean values ± SD for the fetal circulatory variables obtained from recordings of aortic blood flow velocity and diameter synchronized by fetal ECG

Gestational age (wk)	*Site of measurement*	*n*	*FHR (beats/min)*	*V (cm/s)*	*Q (ml)*	*Q (ml/kg)*	*Deff (mm)*	*Dmean (mm)*	$\frac{Deff - Dmean}{Dmean}$ (%)
28-29	Dia	6	144.0 ± 5.8	31.1 ± 5.4	2.4 ± 0.9	2.1 ± 0.9	4.84 ± 0.60	4.66 ± 0.6	3.9
	Bif	5	144.6 ± 6.2	35.2 ± 5.9	2.4 ± 0.5	2.0 ± 0.7	4.59 ± 0.44	4.46 ± 0.41	2.9
33-34	Dia	8	138.0 ± 10.0	29.8 ± 5.4	3.6 ± 0.8	1.7 ± 0.4	6.00 ± 0.90	5.83 ± 0.87	2.9
	Bif	10	139.6 ± 7.2	34.8 ± 5.0	3.3 ± 0.8	1.5 ± 0.3	5.24 ± 0.45	5.11 ± 0.43	2.5
38-39	Dia	8	143.0 ± 11.4	33.4 ± 4.6	5.6 ± 1.5	1.9 ± 0.6	7.08 ± 0.70	6.90 ± 0.68	2.6
	Bif	8	143.1 ± 9.9	32.1 ± 4.3	4.3 ± 1.1	1.4 ± 0.4	6.38 ± 0.75	6.26 ± 0.79	1.9

n, Number of accepted recordings; *V*, mean blood flow velocity; *Q*, aortic stroke volume; *Deff*, effective diameter; *Dmean*, mean diameter; *Dia*, just above the level of the fetal diaphragm; *Bif*, just above the level of the bifurcation.

Table II. Mean values ± SD for the time interval between the QRS complex and onset of the velocity cycle, onset of the diameter cycle, maximum of the velocity cycle, and maximum of the diameter cycle

Gestational age (wk)	*Site of measurements*	*n*	*TstartV*	*TstartD*	*TmaxV*	*TmaxD*	$\frac{TmaxD - TmaxV}{TmaxV}$ (%)
28-29	Dia	6	43 ± 5	46 ± 7	108 ± 6	160 ± 9	48
	Bif	5	50 ± 10	52 ± 5	111 ± 10	155 ± 5	40
33-34	Dia	8	47 ± 8	51 ± 10	113 ± 13	167 ± 11	48
	Bif	10	60 ± 13	63 ± 11	122 ± 15	172 ± 15	41
38-39	Dia	8	57 ± 16	55 ± 10	120 ± 23	175 ± 15	46
	Bif	8	63 ± 14	64 ± 13	125 ± 13	169 ± 13	35

n, Number of accepted recordings; *Dia*, just above the level of the diaphragm; *Bif*, just above the level of the bifurcation; *TstartV*, onset of the velocity cycle; *TstartD*, onset of the diameter cycle; *TmaxV*, maximum of the velocity cycle; *TmaxD*, maximum of the diameter cycle.

nor the time lag between velocity and diameter peak was significantly correlated to FHR.

Comment

Noninvasive measurements with the use of combined Doppler and real-time ultrasonographic techniques,[1, 11] are extensively used for fetal blood flow studies in obstetrics. The estimation of peripheral resistance in the fetal and placental circulation on the basis of various waveform parameters and indices calculated from registrations of blood flow velocity[12-14] has been of particular interest. When calculating volume blood flow from blood flow velocity and vessel diameter one has to be aware of certain technical drawbacks. For instance, simultaneous measurement of blood flow velocity and vessel diameter with independent ultrasonographic equipment is impossible because of ultrasonographic interference. A method for the synchronization of blood flow velocity and diameter curves with fetal ECG signals has been applied for the study of the time difference between the velocity and the diameter traces and for the study of the accuracy of volume blood flow estimation at the thoracic and abdominal levels of the fetal aorta during the course of the third trimester.

In the present study the values of mean blood flow velocity and weight-related aortic stroke volume corresponded fairly well to earlier findings.[6, 15] The quite small time lags between the curves for onset of velocity and diameter, consistent with data from Lingman et al.[6] at both levels and in all three gestational periods, are probably insignificant in view of the time resolution limit of the digitizer used for the analysis. Thus the onset of the systolic blood flow velocity increase and the vessel expansion can probably be regarded as simultaneous. Lingman et al.[6] showed both a significant time difference between the systolic velocity peak and the diameter peak and an accompanying larger effective diameter, compared with the means of systolic and diastolic diameter, at the thoracic level of the aorta in term fetuses. In our study the mean blood flow velocity peak occurred significantly earlier than the diameter peak at both the thoracic and the abdominal level in all three gestational periods investigated, the difference being more pronounced than that previously reported.[6]

The main source of error in the calculation of volume blood flow is probably the measurement of the vessel diameter.[2] The time lag between the velocity and the diameter courses is usually not taken into account. The differences between the effective and the mean aortic diameter in the present study caused an underestimation of the volume blood flow both in the thoracic and in the abdominal aorta. The relative significance of the difference seems to be slightly greater in earlier pregnancy and in the thoracic aorta than in term pregnancy and in the abdominal part of the vessel, the volume error values being 7.9%, 5.9%, and 5.3% in the

thoracic aorta and 5.9%, 5.5%, and 3.9% in the abdominal aorta in the respective gestational period. The blood flow error reported by Lingman et al.[6] for the term fetuses was 6%.

The tendency toward a less pronounced relative time difference between the peak of the velocity curve and of the diameter curve in the abdominal aorta, vis-a-vis the thoracic part of the fetal aorta, in our study can probably be attributed to a decreasing crest time (time from the onset to the peak of the diameter curve) with increasing distance from the heart, as earlier described in the fetus by Sindberg Eriksen et al.[16] No obvious time-lag differences, conceivably resulting from changes in viscoelastic properties in the fetal aorta with increasing gestational age, were seen.

The study has confirmed earlier results[6] and has given preliminary information on longitudinal trends in the course of pregnancy. The error caused by the nonsimultaneous measurements of blood flow velocity and diameter and by use of the mean diameter instead of the effective diameter in calculation of volume blood flow was found to be <8% and thus probably of little practical importance.

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Blood pressure measured telemetrically from home throughout pregnancy

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Sixty-eight healthy pregnant women measured their blood pressure at home for 1 day every 4 weeks from 14 weeks' gestation until delivery. Blood pressure measurements were made with the Cambridge blood pressure telemetry system, which was composed of a Dinamap 1846 monitor linked to and controlled by a dedicated microprocessor which communicated transtelephonically with a hospital-based microcomputer. On each measurement day each woman measured her blood pressure five times: on first rising and then at 10 AM, 2 PM, 6 PM and 10 PM. At each measurement session the blood pressure was automatically taken 10 times at 1-minute intervals. A total of 23,790 individual blood pressure measurements were analyzed. Systolic, diastolic, and mean arterial blood pressures were lowest at 18 weeks' gestation, rising slowly thereafter at a rate of 0.4 mm Hg systolic and 0.2 mm Hg diastolic per week. The maternal pulse rate also increased steadily after 18 weeks at a rate of 0.25 beats/min per week. There was a strong correlation between the blood pressures at 18, 26, and 38 weeks. All blood pressure parameters were significantly lower on first rising than at other times of the day, although the differences were small: 5 mm Hg for systolic, 4 mm Hg for mean arterial, and 3 mm Hg for diastolic blood pressure. After 10 AM, however, there was no significant daytime variation in any blood pressure parameter, indicating that for most purposes the time of day at which pressure measurements are made is unimportant. (AM J OBSTET GYNECOL 1990;163:30-6.)

Key words: Pregnancy, blood pressure, telemetry, computer, Dinamap, home care

Ever since the association between eclampsia and hypertension was first recognized, the measurement of blood pressure throughout pregnancy has become an essential part of good antenatal care. However, before an abnormality in blood pressure can be recognized, a normal range must first be defined.

The principal aim of this study was to determine the range of blood pressure throughout pregnancy. A secondary aim was to determine whether there is any significant variation in blood pressure at different times of the day. For the purpose of this study we used a computerized system for the telemetry of maternal blood pressure from home.

Although there are many published studies in this field,[1-7] all are based on data collected in the hospital or the obstetrician's office. No previous study has measured the blood pressure throughout pregnancy in the woman's normal environment, her own home. Furthermore, no previous study has included measurements made at different times of the day throughout pregnancy.

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Patients, equipment, and methods

Patients. We recruited 68 women who lived within a 30-mile radius of the Rosie Maternity Hospital in Cambridge, and who first attended the antenatal clinic before 14 weeks' gestation as determined by the date of their last menstrual period. Patients were recruited sequentially (in the order in which they attended the booking clinic). No attempt was made to select normal pregnancies for inclusion in the study, or to exclude women with hypertension or other medical problems.

Equipment. The home telemetry equipment consisted of a Dinamap 1846SX blood pressure monitor (Critikon, Sunninghill, Berks, U.K.) that was linked to, and controlled by, a microprocessor built to our own specification. The Dinamap monitor uses an oscillometric technique to measure systolic, diastolic, mean arterial blood pressures, and pulse and is of proved accuracy[8] and reliability.[9]

The microprocessor unit contained a single-board microcomputer, an autodialling telephonic modem (able to dial preprogrammed numbers automatically), and an interface through which the monitor was controlled. At each measurement session the micropro-

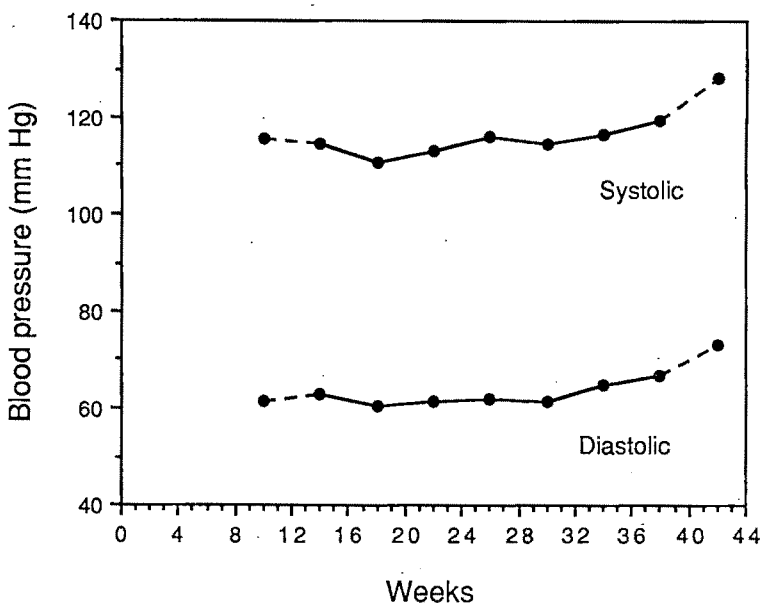


Fig. 1. The changes in systolic and diastolic blood pressures which occurred with gestation, average of all patients. The *dotted* parts of the line indicate regions where the data represent only five patients.

cessor instructed the instrument to make 10 blood pressure determinations at 1-minute intervals, and then memorized the results. When the 10 readings were complete, the microprocessor automatically transmitted the results from the patient's home over the public telephone network to a hospital-based Amstrad (IBM PC-XT compatible) microcomputer (Amstrad, Brentwood, Essex, U.K.). Our blood pressure telemetry system has been substantially improved since it was first described.[10]

Methods. Each woman was taught to use the system herself and was then able to conduct her own automated 10-minute measurement session at home without supervision. During each session the patient sat quietly with the cuff on her right arm, which rested in her lap. In this position the cuff was approximately at the level of the heart. All women measured their blood pressures at home in this way for one complete day every 4 weeks from 14 weeks until delivery. Measurements were made on rising, and then at 10 AM, 2 PM, 6 PM, and 10 PM. Women were encouraged to rest for 5 minutes before each measurement session.

To avoid any possibility that the results of home blood pressure measurements could influence clinical management, the results of home blood pressure readings were not shown to patients' own obstetricians.

All gestational ages were calculated from an ultrasonographic measurement of biparietal diameter at approximately 18 weeks. To determine any trend with gestational age, blood pressure and pulse data were averaged over 4-week epochs. Data were analyzed with the SPSS/PC program.

Results

There were 26 nulliparous and 42 parous women with an average age of 26.7 years (range, 19 to 39 years). All were white with singleton pregnancies and none were receiving any medication (other than iron or vitamins). The ages of the parous and nulliparous women were not significantly different. A total of 2379 measurement sessions were made. Each session consisted of 10 measurements; thus 23,790 individual measurements of blood pressure and pulse were made.

Blood pressure measurements began at 14 weeks' after the last menstrual period, before gestational ages had been established ultrasonographically. In five pregnancies the ultrasonographically determined gestational ages were substantially less than had been suggested by the duration of amenorrhea, and for this reason the data from these women begin at 10 weeks' gestation.

Ten women did not complete their 38-week blood pressure measurements; six went into spontaneous labor, three underwent elective cesarean section, and labor was induced in one. Fifty-three women were delivered between 38 and 42 weeks; 31 went into spontaneous labor, six had elective cesarean sections, and in five labor was induced. Two women were admitted to the hospital at 38 and 39 weeks' gestation because hypertension (150/90 and 160/100 mm Hg, respectively)

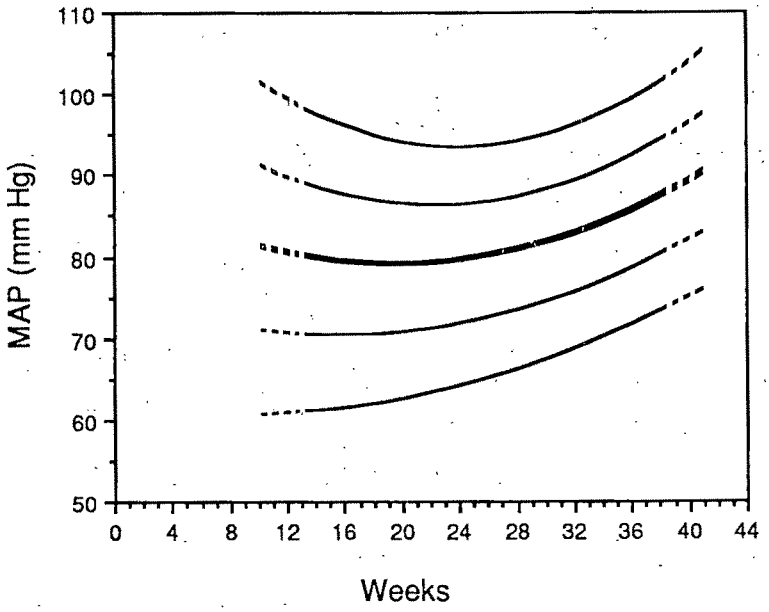


Fig. 2. Smoothed curves show the changes in mean arterial pressure that occurred with gestation, averages of all patients. The *thick line* is the 50th percentile, the *thinner lines* above and below represent ±1 and 2 SDs. The *dotted* parts of the line indicate regions in which the data represent only five patients.

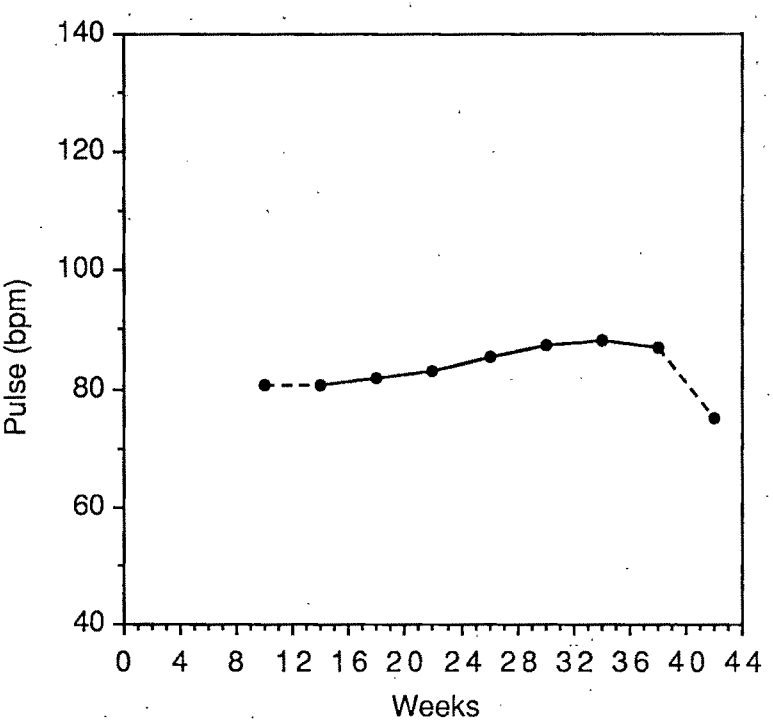


Fig. 3. The changes in pulse rate which occurred with gestation (averages of all patients). The *dotted* parts of the line indicate regions where the data represent only five patients.

was detected with a conventional mercury sphygmomanometer in the antenatal clinic, and labor was subsequently induced.

Only five women completed blood pressure sessions at 42 weeks' gestation. Because of the small numbers of patients providing 10-week and 42-week blood pressure results (five in each case), the data from these gestational ages should be interpreted with caution.

Blood pressure and pulse changes with maternal

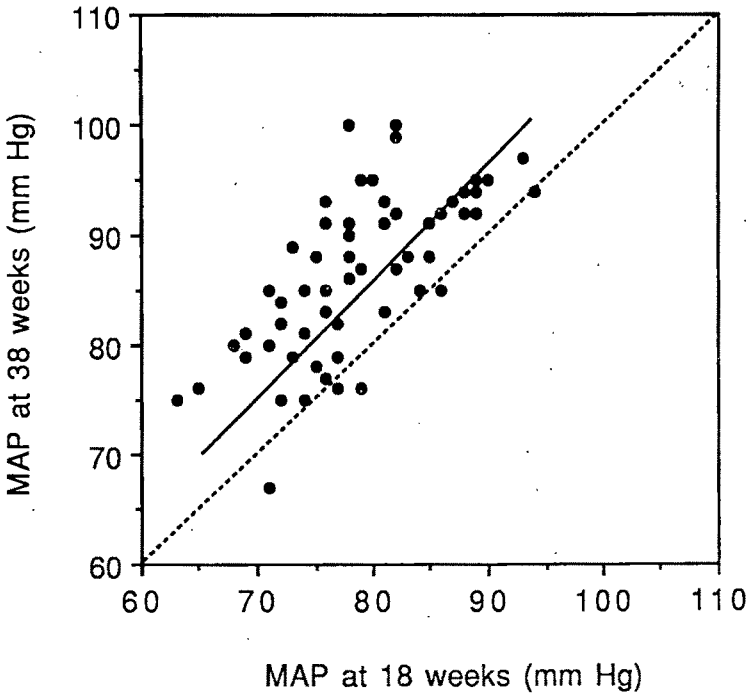


Fig. 4. Mean arterial pressure at 38 weeks' gestation plotted against mean arterial pressure at 18 weeks for all patients. *Dashed line,* Line of equality; *solid line,* correlation line.

age and parity. We found no correlation between maternal age and any blood pressure parameter or pulse rate. There were no significant differences in blood pressure or pulse rate between parous and nulliparous women at any gestational age, and therefore we combined the data from both groups.

Blood pressure and pulse changes with gestational age. Fig. 1 shows the systolic and diastolic blood pressures averaged over 4-week epochs throughout pregnancy. The lowest readings were obtained at 18 weeks' gestation: 111 mm Hg systolic and 61 mm Hg diastolic on average. Pressures slowly increased thereafter, and by 38 weeks'gestation they had reached averages of 119 mm Hg systolic and 65 mm Hg diastolic, average increases of 0.4 and 0.2 mm Hg per week, respectively. Fig. 2 shows the trend in mean arterial pressure throughout pregnancy, averaged over all patients, together with smoothed curves representing 1 and 2 SDs above and below the mean.

Fig. 3 shows the average pulse rate in 4-week epochs throughout pregnancy. The pulse increases from 82 beats/min at 18 weeks to 87 beats/min at 38 weeks, an increase of 0.25 beats/min per week.

We found strong correlations between the mean arterial pressure at 18 and 38 weeks ($r = 0.60$, $p < 0.0001$) and the mean arterial pressure at 26 and 38 weeks ($r = 0.69$, $p < 0.0001$) as illustrated in Figs. 4 and 5, respectively. In both figures the correlation line and the line of equality are shown to demonstrate the blood pressure shift that occurs from the earlier to the later gestation in each case. We found similar relationships with systolic and diastolic pressures (data not shown, $p < 0.0001$ in all cases).

Blood pressure and pulse changes with time of day. Fig. 6 shows the changes in blood pressure that occurred during the day. As can be seen, the systolic, diastolic, and mean arterial pressures were significantly lower on first rising than from 10 AM and afterward ($t = -6.3, -3.3, -3.9$ and $p < 0.001, 0.01, 0.001$), although the differences were small: 5, 3, and 4 mm Hg, respectively. After 10 AM there was no significant change in any measure of blood pressure.

Fig. 7 shows that the pulse rate was significantly higher from 10 AM to 2 PM than before ($t = 8.5$, $p < 0.001$) or after ($t = 10.8$, $p < 0.001$) these times. Again, the actual difference was small: 4 beats/min.

Comment

This is the first study of blood pressure in normal pregnancy to be based on objective measurements made exclusively in the subjects' own homes, where they are free of the distractions and anxieties that might influence clinic or office measurements.

An automatic machine such as the Dinamap monitor is ideal in epidemiologic studies because it eliminates observer bias, digit preference, and intraobserver and interobserver variation[11] that have weakened studies with the conventional (true zero) mercury sphygmo-

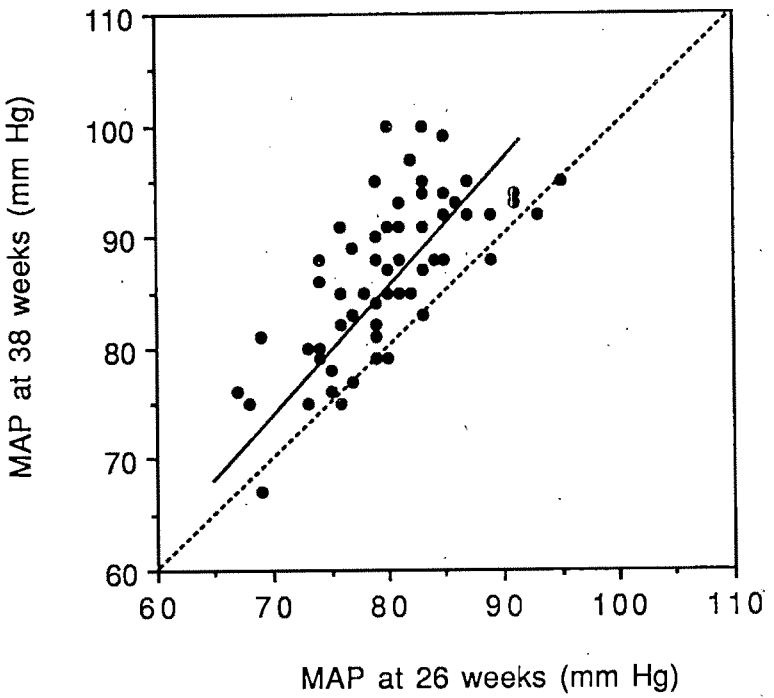


Fig. 5. Mean arterial pressure at 38 weeks' gestation plotted against mean arterial pressure at 26 weeks for all patients. *Dashed line,* Line of equality; *solid line,* correlation line.

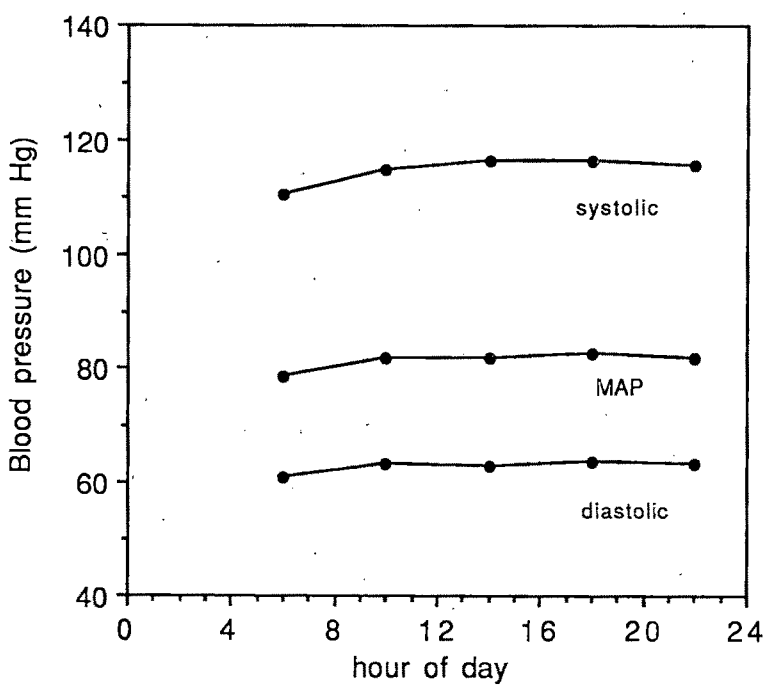


Fig. 6. The changes in systolic, diastolic, and mean arterial pressure which occurred during the day (averages of all patients).

manometer,[4, 5, 7] and it is capable of remote control by a microprocessor system. The American Heart Association has recommended that phase V of the Korotkoff sounds be used to determine the diastolic end point when auscultatory methods are used to determine blood pressure.[12] This advice is often difficult to follow in pregnancy because phase V is commonly absent[3] hence obstetricians generally use phase IV instead. De-

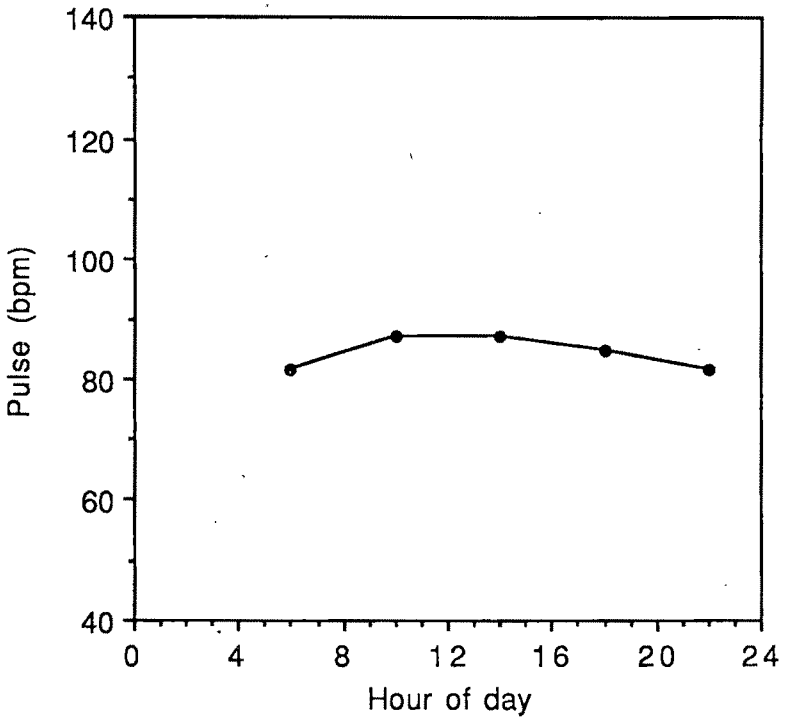


Fig. 7. The changes in pulse rate which occurred during the day (averages of all patients).

vices such as the Dinamap that use an oscillometric technique to determine the blood pressure do not rely on the Korotkoff sounds, and should give equally accurate results in pregnant and nonpregnant subjects.

When blood pressure trends are determined throughout pregnancy, some authors[2, 6, 7] have deliberately excluded from their studies patients whose hypertension developed eventually. However, because most pregnant women in whom a blood pressure >140/90 mm Hg develops may simply represent the upper extreme of a normal distribution, rather than have genuine preeclampsia, their exclusion from analysis will give a misleading picture of the blood pressure of the pregnant population in general. We have therefore included data from all our patients, regardless of whether they met the clinical diagnostic criteria for "preeclampsia." However, even if we had excluded blood pressure data from those patients with hypertension, we would have only slightly reduced our average pressures through pregnancy because only two of our patients came into this category, and they both provided data from 14 to 38 weeks' gestation.

The blood pressure readings we obtained were lower than those reported by Henry,[1] Andros and Arbour,[2] Page and Christianson,[3] and Wilson et al.[5] who used conventional sphygmomanometers, and Moutquin et al.[6] who used a Dinamap monitor, and higher than those reported by McGillivray et al.,[3] who used the London School of Hygiene sphygmomanometer. The lack of significant daytime variation in the blood pressure after 10 AM is consistent with previous findings in both nonpregnant[13] and pregnant subjects[14, 15] and confirms that, for most purposes, the time of day at which pressure measurements are made is unimportant. Our finding that the blood pressures of parous and nulliparous women are not significantly different is in agreement with the findings of Henry[1] and Moutquin et al.[6]

Large swings of blood pressure may occur over relatively short periods. Dalton et al.[10] found a modal swing of 23 mm Hg in the systolic and 13 mm Hg in the diastolic blood pressure, and a maximum swing of 41 mm Hg in the systolic blood pressure within a period of only 10 minutes in 90 measurement sessions from the homes of pregnant women. Mooney and Dalton[16] measured the blood pressures of a group of 51 hypertensive pregnant women every 5 minutes for 1 hour. They found a mean swing of 24 mm Hg in the systolic and 19 mm Hg in the diastolic blood pressure, and a maximum swing of 50 mm Hg in the systolic and 31 mm Hg in the diastolic blood pressure. A consequence of these findings is that large sampling errors may occur if reliance is placed on single blood pressure measurements. A 10-measurement series, as in our study, minimizes the effect of such errors. The only other study of blood pressure in pregnancy to have addressed the problem of sampling errors is that of Moutquin et al.[6] They used a Dinamap 845 monitor to measure each

woman's blood pressure repeatedly at 2-minute intervals until a discrepancy of less than 5 mm Hg was observed. Their technique, although preferable to single measurements alone, remains prone to sampling errors.

Our results provided good correlations between pressures at 14, 26, and 38 weeks' gestation. A 10-minute Dinamap pressure screen at approximately 18 weeks' gestation may be more useful in predicting patients in whom hypertension will develop during late pregnancy than were earlier screening tests based on "one-off" pressure measurements made in the office.[17] However, a large prospective trial is necessary to evaluate the predictive usefulness of such 10-minute pressure screening, whether performed in the obstetrician's office or in the patient's home.

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β-Adrenergic receptor blockade in the management of pregnant women with mitral stenosis

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Twenty-five pregnant women with symptomatic mitral valve stenosis (mean valve area, 1.1 ± 0.25 cm^2) were managed by initiation or modification of β-adrenergic receptor blockade with the use of either propranolol or atenolol. Significant improvement of symptoms occurred in 23 patients (92%) ($p < 0.01$); the mean maternal heart rate was reduced significantly from 86 ± 4 to 78 ± 5 beats/min ($p < 0.0001$). The overall fetal heart rate ranged between 130 to 150 beats/min during treatment. Only two patients required urgent closed mitral valvotomy, after pulmonary edema developed as a result of poor compliance to β-blockade. All patients were safely delivered of infants at term. Fetal heart rates ranged between 120 to 140 beats/min at delivery. There was no maternal or fetal death. Pregnant woman with symptomatic mitral valve stenosis can be safely managed with β-blockade, giving significant reduction in the incidence of pulmonary edema with no unwanted neonatal side effect. (Am J Obstet Gynecol 1990;163:37-40.)

Key words: Mitral stenosis, pregnancy, β-adrenergic receptor

Mitral stenosis continues to be the most common rheumatic valvular lesion encountered in pregnancy, particularly in developing countries. Cardiac surgery during pregnancy presents a risk to both fetus and mother, and should be performed only when absolutely necessary.[1,2]

This study shows that symptomatic pregnant women with moderate to severe mitral stenosis can be managed conservatively by β-adrenergic receptor blockade without the need of exposure to the risk of closed mitral valvotomy.

Patients and method

Between June 1985 and June 1988, 25 pregnant woman with moderate to severe mitral stenosis (mitral valve area range, 0.6 to 1.5 cm^2; mean, 1.1 ± 0.25 cm^2) were delivered of infants in the Armed Forces Hospital, Riyadh, Saudi Arabia. Their ages ranged from 15 to 40 years (mean, 28 years).

Before pregnancy 72% of the patients were symptomatic: seven were in New York Heart Association (NYHA) class I, 14 in class II, and four in class III. In all 25 patients, symptoms either developed or became more severe during pregnancy; three patients were in NYHA class I but had palpitations, 12 were in class II, seven in class III, and three in class IV (Fig. 1). Before pregnancy one third of patients had palpitations in addition to shortness of breath; the palpitations became worse during pregnancy. Palpitations developed in an additional one third during the pregnancy.

During pregnancy all patients were in sinus rhythm and had clinical evidence of moderate to severe mitral stenosis; eight patients also had mild aortic regurgitation, seven had mild mitral regurgitation, and four had mild tricuspid regurgitation. In all patients the nature of the underlying cardiac lesion was already documented, either by two-dimensional echocardiogram and Doppler ultrasonographic studies before and during pregnancy or by cardiac catheterization before pregnancy.

All patients were followed-up in a combined antenatal and cardiac clinic at 4-week intervals in the first and second trimester and at every 2 weeks in the last trimester. At each visit the patient had a complete physical examination. Maternal heart rate and blood pressure, fetal position and presentation, and fetal heart rate were recorded throughout pregnancy; the mean values for each patient are shown in Table I.

Before pregnancy two thirds of the patients were receiving digoxin 0.25 mg once daily in addition to a diuretic, either hydrochlorothiazide 25 mg daily or frusemide 40 mg daily. β-Blockade was given as new therapy during the pregnancy in 16 patients; 14 of these

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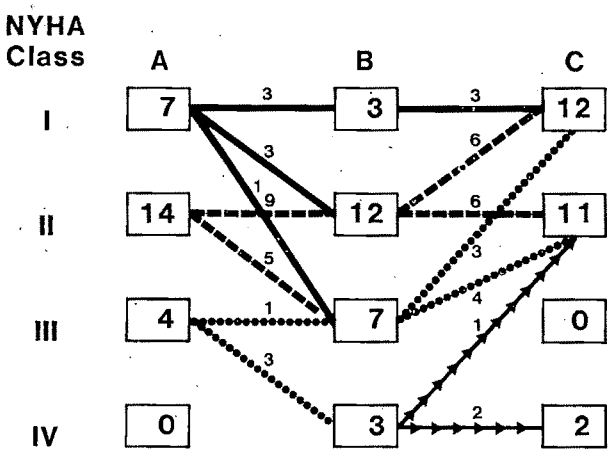


Fig. 1. New York Heart Association class *(NYHA)* changes in symptomatology: **A,** before pregnancy; **B,** during pregnancy before initiation or increase of β-blockade therapy; **C,** during pregnancy after adequate β-blockade. Note significant improvement from **B** to **C** ($p < 0.01$).

constitute group I (pulmonary edema developed in two patients, requiring closed valvotomy). In nine patients already receiving either propranolol or atenolol, β-blockade dosage was increased (group II). Overall, atenolol 100 to 200 mg daily was administered to 11 patients and propanolol 10 to 80 mg was administered three times daily to 14 patients.

Patients were routinely admitted to the hospital 3 to 7 days before the expected date of delivery, except for one patient with severe mitral stenosis (mitral valve area, 0.9 cm^2), who was admitted for the entire third trimester.

Statistics. Data are expressed as a mean ± SD. The paired Student t test and χ^2 square test were used to test the difference between means.

Results

During pregnancy before initiation or increase of β-blockade therapy, 15 patients were in either NYHA class I or II and 10 were in either class III or IV. After initiation or modification of previous β-blockade, 23 patients (92%) improved significantly to either class I or II ($p < 0.01$) (Fig. 1). Two patients (8%) with severe mitral stenosis (mitral valve areas, 0.6 and 1 cm^2, respectively, assessed by continuous-wave Doppler ultrasonography) had poor complicance to β-blockade, with heart rates not reduced below 90 beats/min. Pulmonary edema developed in both patients. Hypotension developed in the first patient after a small dose of propranolol, without control of her heart rate; she had a closed mitral valvotomy in the second trimester. The second patient was admitted in pulmonary edema twice; during the second admission in the second trimester she underwent closed mitral valvotomy. Both pregnancies continued to a safe vaginal delivery. In the remaining 23 patients the overall mean maternal heart rate was reduced significantly from 86 ± 4 to 78 ± 5 beats/min. In group I the reduction was from 88 ± 3 to 78 ± 5 beats/min ($p < 0.001$) after initiation of β-blockade therapy; in group II, after increased β-blockade therapy, the mean maternal heart rate was reduced from 84 ± 3 to 77 ± 5 beats/min ($p < 0.005$). Overall, the fetal heart rate ranged between 130 to 154 beats/min during β-blockade treatment (Table I).

All 25 patients had a vertex presentation and were safely delivered after 37 to 39 weeks' gestation. Twenty were delivered vaginally and five were by cesarian section—one because of placenta previa, three because of previous cesarian section, and one because of severe mitral stenosis with pulmonary hypertension in whom it was thought unsafe to attempt vaginal delivery.

For the majority of those patients vaginally delivered of infants the second stage of delivery was short, probably because of the small-sized fetus, but two patients required forceps extraction because of second-stage delay. In two other patients 40 mg of intravenous Lasix furosemide preparation was used intrapartum to achieve preload reduction.

The mean weight of the babies was 2.8 ± 0.4 kg (range, 2.1 to 3.5 kg) with a mean Apgar score of 9 (range, 8 to 10) (Table I). The mean heart rate ranged between 120 to 140 beats/min. There was no maternal or fetal death or fetal morbidity in this series. Three patients had mitral balloon valvotomy and one had open mitral valvotomy 2 months after delivery.

Comment

This study shows that β-blockade can be used successfully in the management of pregnant women with moderate to severe, symptomatic, rheumatic mitral stenosis. All were safely delivered of a live infant at term.

The specific hemodynamic changes that occurred during pregnancy are a 40% increase in the cardiac output, a 10% to 20% increase in heart rate, a 30% to 40% increase in the blood volume, and increased irritability of the left atrium. The latter may precipitate fast atrial fibrillation, particularly in patients with mitral stenosis.[3] The primary hemodynamic effect of severe mitral stenosis is obstruction of blood flow from the left atrium to left ventricle during diastole. Tachycardia, or fast atrial fibrillation, will increase both the left atrial and subsequently pulmonary vascular pressures, leading to pulmonary edema. In this study the main objective was to control the maternal heart rate, maintaining a rate of 70 to 86 beats/min, particularly during any effort. This was achieved with β-blockade except in two patients with poor compliance to the therapy

Table I. Clinical characteristics of mother and fetus during pregnancy

Patient	Age (yr)	Mean maternal heart rate (beats/min)		Mean systemic blood pressure (mm Hg)	Mitral valve area (cm^2)	Mean fetal heart rate	Baby weight	Type of delivery
		Before β-blockade	After β-blockade					
1	26	86	80	110/70	1.1	154	2.8	Vaginal
2	26	80*	70	110/70	1.2	140	2.3	Caesarian Section
3	24	90	80	100/60	0.9	130	3.3	Vaginal
4	37	82*	80	120/60	1.4	130	3.2	Vaginal
5	31	88	80	100/70	1.2	135	2.8	Vaginal
6	27	89*	82	100/70	1.0	132	2.4	Ceasarian Section
7	29	88	75	95/50	1.3	134	2.8	Ceasarian Section
8†	20	110	130	90/55	0.6	136	3.2	Vaginal
9	15	84	72	95/60	0.9	158	2.9	Vaginal
10	34	88	86	110/70	0.9	130	3.3	Ceasarian Section
11	27	86	80	110/71	1.1	135	2.4	Vaginal
12†	30	100	110	120/80	1.5	145	3.5	Vaginal
13	30	82*	70	110/00	0.7	140	3.2	Vaginal
14	30	82*	80	110/70	1.1	144	3.5	Vaginal
15	33	94	85	120/80	1.5	140	3.1	Vaginal
16	25	92	85	110/70	1.3	135	2.7	Vaginal
17	31	90	80	110/80	1.4	130	2.8	Vaginal
18	33	84*	78	115/80	0.9	140	2.1	Vaginal
19	23	92	80	110/70	1.5	150	3.1	Vaginal
20	18	84	72	100/70	0.9	134	2.2	Vaginal
21	30	86	80	110/60	1.1	140	2.8	Vaginal
22	23	84*	80	110/70	1.5	140	2.7	Vaginal
23	40	86	70	110/70	1.3	136	2.6	Vaginal
24	25	88*	80	110/75	1.1	140	2.2	Vaginal
25	28	82*	73	110/70	1.0	138	2.4	Ceasarian section

Mean maternal heart rate ± SD = 86 ± 4 before and 78 ± 5 after adequate beta blockade, excluding patients 8 and 12.
*Group II (9 patients) who already were receiving β-blockade before pregnancy, and the dosage subsequently modified.
†Patients 8 and 12 underwent closed mitral valvotomy.

whose heart rates were >100 beats/min before treatment and were not lowered to <90 beats/min after treatment. Control of the heart rate prevents the increase in pulmonary wedge pressure with a consequent increase in mitral valve gradient, which may precipitate pulmonary edema.

Szekely[4] reported an overall mortality of 1% in all patients with mitral stenosis in pregnancy, regardless of NYHA classification; in severe cases (NYHA class III or IV) maternal mortality rises to 4 to 5%. In the presence of atrial fibrillation, mortality further increases significantly to 17%.[5] In our series there were no deaths, despite the fact that two thirds of the patients had severe mitral stenosis (mitral valve area, <1.1 cm^2).

Closed mitral valvotomy in pregnancy is not without maternal or fetal morbidity or mortality. In 29 patients who underwent closed mitral valvotomy during pregnancy, one maternal and two neonatal deaths were reported.[6] Vosloo[7] and Zitnik[8] reported fetal mortality of 12.2% and 33%, respectively, after mitral valvotomy during pregnancy. On the other hand, closed mitral valvotomy may be lifesaving in cases of medically uncontrolled pulmonary edema during pregnancy. Only two of the patients in this report underwent closed mitral valvotomy during pregnancy because of pulmonary edema as a result of poor compliance to medication, with no fetal or maternal death.

This study shows that β-blockade decreases the risk of development of pulmonary edema, which is the most important cause of maternal mortality[9, 10] during pregnancy. Previously published reports concerning the use of propranolol during pregnancy seem contradictory. Koliobash[11] and Turner[12] used propranolol in hypertrophic cardiomyopathy during labor; they reported no side effects on the neonates who were recorded as healthy at birth. However, Reed[13] and Goldstone[14] reported individual cases in which the mother received high doses of propranolol during pregnancy and labor for the treatment of hypertension and ventricular tachycardia. The infants had a low Apgar score and hypoglycemia developed, but their subsequent courses were uneventful. The present study revealed no side effects on either the Apgar score or heart rates of the neonates. The weights of most of the newborns in our series were relatively low; this is most likely because of the chronic low cardiac output as a result of mitral stenosis.

In conclusion, we believe that significant mitral stenosis in pregnancy can be safely managed with β-blockade with no unwanted effect on the mother or

neonate. Furthermore β-blockade was shown to reduce the incidence of development of pulmonary edema during pregnancy.

Addendum

Since the completion of this article an additional 20 pregnant women with moderate to severe mitral stenosis have been successfully treated to the completion of gestation with β-adrenergic receptor blockade; none required closed mitral valvotomy.

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Cocaine-related maternal death

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Hemodynamic overload, cardiac ischemia, and arrhythmia are postulated to originate from "sex-cocaine" syndrome resulting in maternal and fetal death. High concentrations of cocaine and metabolites in maternal blood, urine, and nasal secretions confirmed recent ingestion. Changes in the maternal life-style may have contributed to the poor pregnancy outcome. (Am J Obstet Gynecol 1990;163:40-1.)

Key words: Sex-cocaine syndrome, maternal death

Rapid proliferation of cocaine use among women of reproductive age is partially due to unlimited availability of cheaper alkaloid cocaine ("crack"). This produces a life-style particularly inimical to pregnancy.

Cerebrovascular accidents, cardiac arrhythmias, and infarction have resulted in serious illnesses or death in young abusers.[1] High perinatal morbidity and mortality rates are linked to cocaine.[2] Affected neonates demonstrate lifelong neurodevelopmental deficits, recurrent febrile illnesses, and sudden infant death syndrome.

We report a case of both maternal and fetal death related to cocaine in a bizarre cluster of events that unfortunately is likely to recur.

Case report

A 26-year-old black woman, gravida 4, para 3-0-0-3, was brought to the emergency room at University of Miami/Jackson Memorial Hospital Center (UM/JMHC) by Fire Rescue personnel on April 5, 1988. At 2:13 AM they found her unconscious without pulse, respirations, or blood pressure. Electrocardiogram showed severe bradycardia. She was 7 to 8 months

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pregnant and the fetal heart was beating. Intubation, oxygen administration, and mechanical external cardiac massage were immediately established.

On arrival to the hospital at 2:55 AM she was unconscious and cyanotic with no detectable pulse or blood pressure and unresponsive pupils. Electrocardiogram showed asystole. Intravenous ephedrine, bicarbonate, and atropine, external cardiac massage, and mechanical ventilation produced no effect. Simultaneously, obstetric evaluation showed a fetus of 32 weeks' gestation, a tense uterus, and a fetal heart rate of 40 beats/min. There was no blood or amniotic fluid from a long closed cervix. Agonal cesarean section was done, and a female infant was delivered at 2:57 AM, 2 minutes after arrival. There was 30% abruptio placentae. Apgar scores were 1 and 0 (at 1 and 5 minutes, respectively). Infant resuscitation was attempted unsuccessfully for 20 minutes.

Abnormal results from blood drawn on arrival were hemoglobin 10.9 gm/dl and hematocrit 35%. Red blood cell smear showed hypochromia, poikilocytosis, anisocytosis, and basophilic stipling. Base excess of −17 mEq/L, oxygen saturation of 3%, and pH of 6.82 indicated severe acidosis and hypoxemia. In blood obtained directly from the heart, the concentration of cocaine was 0.21 mg/L, benzoylecognine was 1.38 mg/L, and methylecognine was positive. Cocaine and its metabolites were detected in urine and nasal secretions.

The boyfriend said that during sexual intercourse the patient developed intense chest pain, which worsened. Gasping for air, she stumbled to the bathroom and collapsed. He vehemently denied cocaine use.

She had no prenatal care. At 26 weeks' gestation she was seen in the emergency room, complaining of a fall and a painful right hip. The uterus was soft, nontender, and approximated the dates. All vital signs were normal. Follow-up appointment to the prenatal clinic was not kept.

In three previous pregnancies, she was employed, averaged seven prenatal visits, gained 25 to 40 pounds, and was delivered of term-sized female infants. All laboratory studies were normal.

Postmortem findings for both mother and fetus were unremarkable, except for mild lung congestion in the mother. The medical examiner determined that death was caused by cocaine intoxication.

Comment

Cocaine-related maternal deaths are likely to be encountered by obstetricians, because one in every six or seven pregnant women uses cocaine. A prevalence of 12.1% detected at UM/JMHC may be an underestimate.

The medical examiner for Dade County, Florida, investigated 240 sudden, unexpected deaths, 60 of which were due to cocaine overdose while traces of the drug were noncontributory in 180.

Cocaine, an arrhythmogenic and powerful vasoconstrictor, is associated with ischemia in myocardial-cerebral infarction and intestinal gangrene in abusers. The intense anginal pain during sexual intercourse and high blood concentrations of cocaine support the postulate that our patient collapsed from acute cardiac failure that was secondary to ventricular arrhythmia and coronary ischemia. This accounts for the paucity of pathologic conditions found at autopsy.

Acute cardiac events may have been precipitated by "sex-cocaine" syndrome. Sex-induced cardiodynamic surges, higher demands of hyperdynamic circulation of pregnancy, and vasoactive stresses of high levels of cocaine presented a strain sufficient to induce malignant arrhythmia, cardiac failure, and death. Isner et al.[1] suggested that an increase in rate-pressure product may produce these events as a result of ischemia, occurring secondary to a sudden increase in myocardial demand for oxygen, triggered by sexual surges. As cocaine itself impairs oxygen-carrying capacity, further strain on this precariously balanced system will precipitate breakdown. Mother and infant were too obtunded to respond because of intense attenuation of blood flow and oxygenation to vital areas of brain and myocardium.

Contrasting the last pregnancy to previous ones illustrates life-style changes associated with cocaine users, possibly priming her for the terminal events. She was unemployed, sought no prenatal care, and showed suboptimal nutrition in blood smears. Factors inimical to pregnancy outcome besides cocaine include intermittent starvation during cocaine binging, systemic infection, sexually transmitted diseases, multiple "street" drugs, and deterioration of personal grooming, hygiene, and nutrition.[2] The severity of the problems becomes directly proportional to the amount of cocaine abuse. Maternal and fetal death represents an end point.

In animals the death rate from cocaine is twice that of heroin, and in humans unexpected cardiac[1] and neurologic disasters provide compelling evidence that cocaine is the most lethal drug yet abused. Given this, unlimited supplies, willing users, and our failure to recognize cocaine-abusing pregnant women, major catastrophies are certain occurrences.

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Systemic cystic angiomatosis in pregnancy: A case presentation and review of the literature

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Systemic cystic angiomatosis is the involvement of multiple organ systems with a congenital vascular malformation. A combination of vascular anomalies, namely lymphangioma and hemangioma, can coexist. The liver, spleen, kidney, and colon are the most commonly affected organs. The clinical presentation varies and generally reflects the involved organ system. A case of systemic cystic angiomatosis involving the spleen, liver, and kidney is presented. The diagnosis and management during pregnancy is discussed. (AM J OBSTET GYNECOL 1990;163:42-5.)

Key words: Pregnancy, systemic, cystic, angiomatosis

Lymphangiomatosis is a rare congenital malformation of the lymphatic system that generally is first seen during childhood and in young adults.[1] The term systemic cystic angiomatosis is used when the process involves multiple organ systems. The liver, spleen, kidney, and colon are the most commonly affected organs. Occasionally a combination of vascular anomalies, namely, lymphangioma and hemangioma, can coexist. Fink described the first case with spleen involvement in 1885. By 1979 fewer than 10 cases of systemic cystic angiomatosis that involved the spleen have been reported in the world literature. We present the first case of systemic cystic angiomatosis diagnosed with ultrasonography during pregnancy, a review of the literature, and our recommendation for management.

Case report

A 35-year-old white female, gravida 7, para 4, was first seen at 16 weeks' gestation with severe left upper quadrant pain of 3 months' duration associated with low-grade fever. Her medical history was significant for left nephrectomy in 1979 because of persistent hematuria. The pathologic findings were compatible with a cavernous hemangioma of the kidney.

Physical examination on admission revealed a well developed female in moderate distress with a tender, mobile left upper quadrant mass with a lower edge that was palpable 12 cm below the left costal margin; the bowel sounds were normal. There was no evidence of lymphadenopathy. Fundal height was appropriate for 16 week's gestation and fetal heart rate was normal.

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Initial laboratory data included the following: hematocrit 37%, platelet count 135,000, prothrombin time 9.2 (control 4.6), negative direct and indirect Coomb's test results, O positive blood type, and burr cells and decreased platelets on peripheral smear. Hemoglobin electrophoresis, hepatic and renal function studies, screening for collagen vascular disease, febrile agglutinins, carcinoembryogenic antigen, and α-fetoprotein were all within normal limits. Bone marrow findings were consistent with normal cellularity.

Abdominal ultrasonography confirmed an enlarged spleen with extensive cystic changes (Fig. 1). There was also an area of increased attenuation on the right aspect of the liver, suggestive of an intrahepatic lesion. Pelvic ultrasonographic examination confirmed a 16-week intrauterine pregnancy. The preoperative diagnosis was mild hypersplenism, probably a result of congenital cystic spleen.

The patient underwent exploratory laparotomy at 18 weeks' gestation with general anesthesia. An enlarged spleen (615 gm) measuring 17 × 12 × 7 cm was found at surgery. The irregular external surface was characterized by multiple cysts that measured 0.5 to 7 cm in diameter and contained clear or hemorrhagic fluid. The histopathologic findings were compatible with mixed lymphangioma and hemangioma structures (Figs. 2A and 2B).

The remainder of her pregnancy was uneventful. She had a normal spontaneous vaginal delivery of a male infant with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively, and a birth weight of 3945 gm.

Comment

Cystic lymphangiomatosis is a benign congenital vascular malformation frequently seen in infancy and childhood. Histologically it comprises cystic spaces of varying sizes lined by endothelium and surrounded by connective tissue. Any combination of capillary, venous, arterial, and lymphatic components can occur.[1]

The pathogenesis of these lesions remains contro-

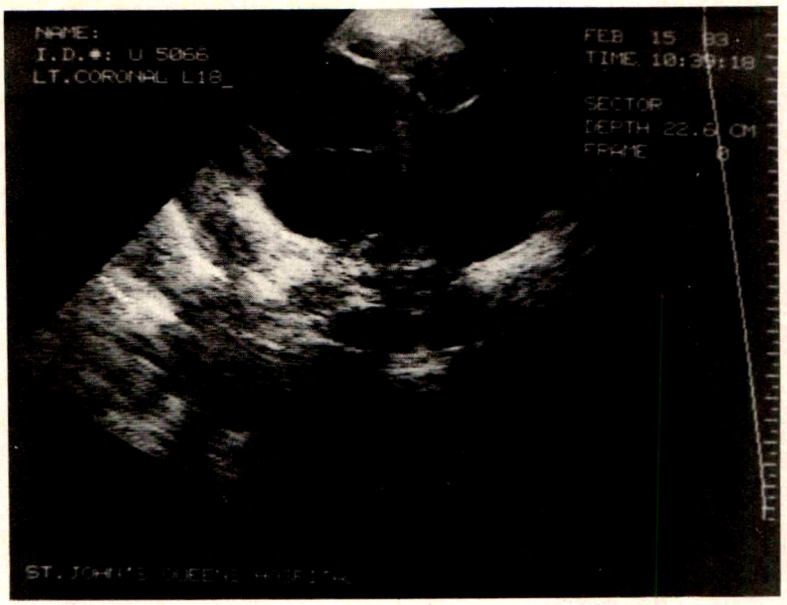


Fig. 1. Ultrasonographic view of spleen illustrates hypersplenism and extensive cystic changes.

versial. Nevertheless some authors believe that these tumors develop as areas of localized lymphatic stasis because of a congenital blockage of the regional lymphatic drainage. There is a female preponderance of these tumors and 80% to 90% are detected before the end of the second year after birth.[1]

If the lymphangioma is part of a generalized disorder with cystic involvement of many organs and tissues the term systemic cystic angiomatosis is used.

Different organs have been involved including mesentery, liver, spleen, kidney, lung, mediastinum, pericardium, skeletal system, and somatic soft tissue. The clinical presentation varies depending on which organ system is involved.[1, 2] Patients with splenic lymphangioma could be asymptomatic or symptomatic at the time of diagnosis. The most common symptom is left upper quadrant pain as a result of enlarging abdominal mass. Other signs and symptoms include nausea, vomiting, weight loss, hypertension, hypersplenism, and consumptive coagulopathy.[2] This last complication is a result of platelet trapping within an angiomatous cyst. A dramatic resolution of the symptoms is generally observed after surgery.

Our patient had involvement of three visceral organs—kidney, liver, and spleen. The clinical presentation at the time of admission was a result of the splenic involvement of the disease.

The techniques currently in use of the evaluation of the spleen include arteriography, computerized tomography scan, scintigraphy, and ultrasonography. The radionuclide and computerized tomography scan can show splenomegaly with multiple focal defects. A "Swiss cheese" appearance on angiography has been considered pathognomonic of splenic cystic lymphangiomatosis. Sonography is a simple and informative, noninvasive technique that can confirm the cystic nature of the lesion and identify involvement in other organs without the use of dyes or radiation.

The differential diagnosis of cystic diseases of the spleen includes parasitic cysts, epithelial lined cysts, and malignancies. The preoperative workup in our patient was not suggestive of a malignancy, but the final diagnosis can be verified only after surgery.[1]

One advantage of performing the surgery in a controlled situation is the prevention of splenic rupture later in pregnancy. This dangerous complication was first reported in a pregnant woman in 1803 by Saxtorph. Buchsbum reviewed 72 cases of splenic rupture during pregnancy and found that most of the affected patients were multiparous and 60% of the ruptures occurred during the third trimester or intrapartum. The presence of a malformed spleen carries a higher risk for spontaneous rupture. The maternal mortality in his series (15.4%) was a result of delay in diagnosis. The perinatal mortality was 70%, and in all cases of surviving infants the splenic rupture occurred before the third trimester.

The postoperative complications of splenectomy are subphrenic abscess, thrombocytosis, and infection. Abscess formation is more common in patients undergoing splenectomy for trauma. The occurrence of thrombocytosis seems to be related to the underlying disease. Its incidence ranges between 7% to 70%. In general, patients with hypersplenism have a higher risk of this complication. Asplenic patients are also at risk of the development of overwhelming infections. This

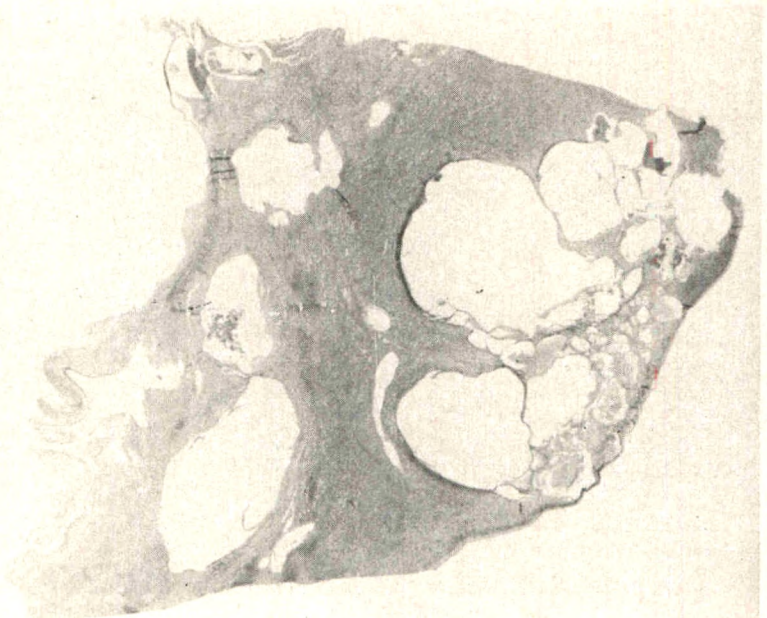


Fig. 2A. Histopathology of spleen illustrates multiple cystic changes on external surface.

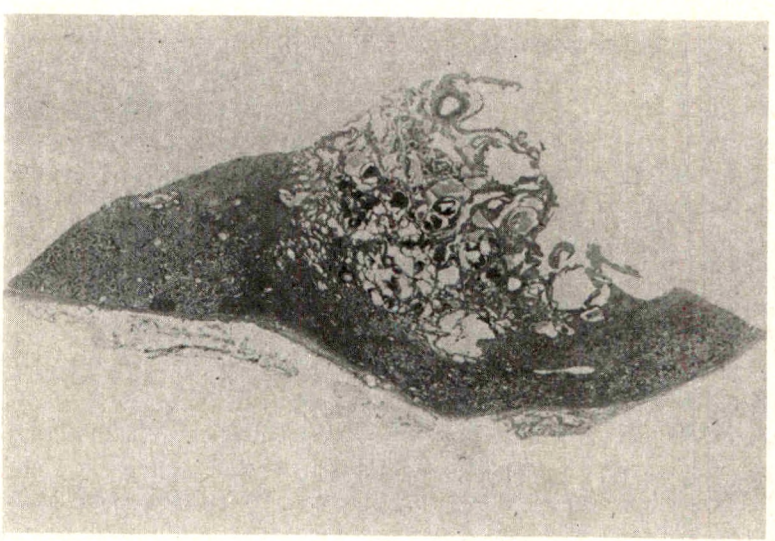


Fig. 2B. Cysts are filled with clear or hemorrhagic fluid compatible with mixed lymphangioma and hemangioma of spleen.

increased predisposition to infection is a result of defective or decreased production of immunoglobulins, a delayed macrophage mobilization, and a defective phagocytosis of pathogenic bacteria. Therefore these patients must be followed up carefully and periodic immunizations should be given as necessary.

Our patient represents a case of symptomatic systemic cystic angiomatosis that was first seen during pregnancy. Sonographic evaluation confirmed the splenomegaly and revealed the cystic nature of that organ. A conservative approach was not advisable because the patient's symptoms worsened during her stay

in the hospital, a benign cause could not be confirmed without tissue pathology, and the possibility of splenic rupture at a more advanced gestational age. It is our belief that the maternal and fetal risks of an emergency splenectomy exceed those of a controlled second-trimester laparotomy.

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Interrelationship between atrial natriuretic factor concentrations and acute volume expansion in pregnant and nonpregnant women

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The secretion of atrial natriuretic factor by human atrial myocytes is stimulated by increased intraatrial pressure or atrial distention. To determine whether acute intravascular volume expansion affects atrial natriuretic factor concentrations during pregnancy, circulating atrial natriuretic factor levels were measured in pregnant women at term (before elective cesarean section) and nonpregnant control subjects before and during intravenous infusion of lactated Ringer's solution (approximately 30 ml/kg). Venous plasma concentrations of α-human atrial natriuretic factor were determined by a specific radioimmunoassay. A significant increase in α-human atrial natriuretic factor levels in nonpregnant subjects was seen. Pregnant women did not show a significant response to a similar stimulus. Finally, basal α-human atrial natriuretic factor levels in pregnant and nonpregnant women were not different. Volume expansion (long-term or short-term) in normal human pregnancy may not be sensed by atrial volume sensors, possibly because it is accommodated by an enlarged maternal vascular compartment. (Am J Obstet Gynecol 1990; 163:45-50.)

Key words: Maternal atrial natriuretic factor concentrations, nonpregnant women atrial natriuretic factor concentrations, volume expansion

Atrial natriuretic factor (ANF) is a hormone secreted by specialized cells in atrial myocytes.[1] ANF demonstrates multiple circulatory and endocrine effects ranging from vasodilation and natriuresis to inhibition of aldosterone and renin production.[2] Increased intraatrial pressure or atrial distention stimulates secretion of ANF. Physiologic or pathologic conditions of central hypervolemia that are secondary to intravascular volume expansion may result in increased secretion of ANF and high circulating levels of α-human ANF (α-hANF).[2]

We have previously shown that during normal human pregnancy maternal ANF levels do not change with advancing gestation.[3] This lack of increase in the maternal plasma ANF concentrations occurs despite a presumed increment in plasma and blood volume during pregnancy. We therefore asked the question whether normal pregnant women at term can respond to an acute intravascular volume expansion with an increase in circulating maternal α-hANF levels and whether there is a difference between their response and that seen in nonpregnant control subjects.

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Table I. Clinical characteristics

	Pregnant (n = 8)	*Nonpregnant (n = 5)*
Age (yr)	29.75 ± 1.95	28.00 ± 1.84
Weight (kg)	88.53 ± 6.30	66.51 ± 2.84*
Gravidity		
0-2	4	5
≥3	4	0
Parity		
0-1	6	3
≥2	2	2
Fluid volume infused (ml)	2556.25 ± 184.06	2030.00 ± 147.99†
Fluid volume infused/body weight (ml/kg)	29.85 ± 1.77	30.66 ± 2.44
Estimated gestational age (wk)	39.44 ± 0.18	NA
Neonatal birth weight (gm)	3862.38 ± 121.03	NA
Anesthesia for delivery		
Epidural	7	NA
Spinal	1	NA

Values are mean ± SEM.
NA; not applicable.
*$p = 0.017$.
†$p = 0.048$.

Material and methods

Patient population. The study was approved by the Clinical Research Practices Committee at the Bowman Gray School of Medicine. All patients signed an informed consent form. There were eight patients at term who were studied before elective cesarean section. There were five nonpregnant subjects who were studied in the proliferative phase of the menstrual cycle. All patients were studied in the morning (7 to 11 AM). They had nothing to eat or drink since the night (10 PM) before. All subjects were normotensive and had no previous history of cardiovascular or renal disease. They were taking no medications except iron and prenatal vitamins (pregnant women). None of the pregnant women were in labor. All underwent cesarean sections while they were under conduction anesthesia.

Volume challenge. In pregnant women who underwent epidural anesthesia, injection of the local anesthetic did not commence until ≥25 minutes. A satisfactory block at the T4 level was achieved by 50 to 60 minutes. Nonpregnant subjects did not undergo conduction anesthesia. All patients were in the left or right lateral decubitus position during the fluid infusion and subsequent observation. We used lactated Ringer's solution as the crystalloid solution for the intravenous volume expansion. For time 0 to 25 minutes, lactated Ringer's solution was infused rapidly. The rate of infusion was 92.5 ± 8.8 ml/min for the pregnant group and 99.3 ± 15.9 ml/min for the nonpregnant group (mean ± SD, differences not significant). The rate of infusion was then tapered off for the remainder of the sampling period.

Blood collection. Venous blood was obtained through an indwelling 19- to 20-gauge catheter and was immediately placed in prechilled ethylenediaminetetraacetic acid containing tubes. The indwelling catheter had been inserted in the arm opposite to the one where the intravenous site was located. Approximately 5 to 10 ml of blood was obtained at various times before and during the intravenous fluid infusion for analytic studies. Blood was kept on ice. Plasma was separated by centrifugation at 4° C and stored at −40° C until analyzed. Under these conditions no significant loss of ANF was noted.

ANF assay. ANF in plasma samples was extracted by a procedure initially described by Brier et al.[4] and validated in our laboratory.[5] A total of 1 ml of plasma and 1.5 ml of 0.1 mol/L acetic acid were mixed. Methanol (2.5 ml) was then added to the extraction tube, and the contents were mixed for 10 minutes. The tubes were then centrifuged at 6000 rpm at 4° C for 20 minutes. The supernatant was poured into a new tube containing 2.5 ml of chloroform and mixed with total inversion for 10 minutes. The tubes were again centrifuged as before. The top (aqueous) layer was removed to a new tube and lyophilized. The extracted samples were stored in −40° C until assayed. They were then allowed to thaw and reconstituted before the assay with 1 ml of 80 mmol/L phosphate buffer (pH 7.4). With this procedure recovery of unlabeled ANF was 54% ± 3%. Recovery was routinely monitored in every assay.

Samples and standards were incubated for 24 hours at 4° C with 100 μl of anti-α-hANF antibody obtained from Dr. Kozo Hashimoto (Department of Internal Medicine, Okayama University Medical School, Okayama, Japan) in 80 mmol/L phosphate buffer (pH 7.4). α-hANF labeled with iodine 125 (5000 to 10,000 cpm/tube) was then added and the tubes were incubated for an additional 24 hours. The antigen-antibody complex was then precipitated with 100 μl of goat antirabbit immunoglobulin G and 100 μl of normal rabbit serum. These tubes were then incubated for 2 hours at room temperature. Phosphate buffer was added and the tubes were centrifuged for 20 minutes at 1500 *g*. The supernatant was decanted and the dried pellets were counted for 5 minutes in a γ-counter. Synthetic α-hANF (Peninsula Laboratories, Belmont, Calif.) (3 to 1000 pg/tube) was used to construct the standard curve. All samples were assayed in duplicate while the standard curve was done in triplicate. The interassay coefficient of variation ranged from 10% to 14% and the intraassay variation was between 6% and 8%. Results were analyzed by means of a four-parameter logistic equation.[6] The 50% inhibitory concentration ranged from 40 to 50 pg/tube. The results are expressed as picograms per milliliter and have been corrected for percent recovery. The conclusions drawn for these results are the same regardless of whether the concentrations have been corrected for the extraction efficiency.

Determinations of serum osmolality and blood hematocrit. Serum osmolality was determined by freezing point depression.[7] The determination of hematocrit was done by the microhematocrit method.[8]

Statistical analysis. Results are presented as mean ± SEM, unless otherwise noted. Statistical analysis was carried out by analysis of variance (repeated measures) and Newman-Keuls test. A value of $p < 0.05$ was considered as significant.

Results

Table I shows selected clinical parameters for the two groups. The two populations of women were similar with regard to age and reproductive history. Although the total volume infused was greater in the pregnant women than in the nonpregnant women when volume was corrected for the subject's body weight, both groups received equivalent volumes of crystalloid. All pregnant women were delivered at term of appropriate-for-gestational-age infants. There were no antepartum intrapartum, or postpartum complications. Seven patients received epidural anesthetics and one patient received a spinal anesthetic. Since a Foley catheter had not been placed in any of these patients, no urine output or solute excretion results are available.

Table II shows ANF concentrations before and after intravenous volume expansion. Basal ANF concentrations in pregnant and nonpregnant women at time 0 were not different. Acute volume expansion with infusion of lactated Ringer's solution resulted in a significant increase in ANF concentrations in nonpregnant subjects only (≥20 minutes compared with time 0). In contrast to the above, pregnant women did not show a significant response to a similar stimulus. The fact that the increase in ANF levels in nonpregnant subjects was first seen at 20 minutes makes it unlikely that conduction anesthesia was a significant confounding variable at that point since the epidural anesthetic was not injected until after 25 minutes. Finally, for times ≥15 minutes, ANF concentrations in the nonpregnant women were higher than those in the pregnant subjects.

Table III shows serum osmolality before and during intravenous volume infusion. As determined in our laboratory, there were no significant differences in serum osmolality between the pregnant and nonpregnant groups of women. This was the case both before and during the intravenous volume infusion.

Table IV shows hematocrit levels before and during intravenous volume infusion. Hematocrit levels at 20 and 50 minutes after the start of the infusion were significantly lower than those seen at time 0. This was true for both the pregnant and nonpregnant groups. Mean arterial blood pressure did not change appreciably during the intravenous infusion (Table V). However, heart rate before and during intravenous volume infusion changed significantly for the pregnant subjects only. There was a significant, albeit moderate, increase in heart rate at 20 and 50 minutes after the start of infusion (Table VI). Since the pregnant subjects had not received the epidural anesthetic at 20 minutes, there is no plausible explanation for this minor increase in maternal heart rate, whereas at 50 minutes peripheral vasodilation might explain the change. Fetal heart rate remained in the normal range throughout the study.

Comment

One of the major physiologic adaptations to pregnancy is the expansion of intravascular and extracellular fluid volume.[9] The underlying mechanisms responsible for this remarkable change are not understood. In an attempt to evaluate the physiologic significance of ANF to human pregnancy and determine whether it is involved in the regulation of the marked volume changes that occur during pregnancy, we have asked the following question: Does long-term

Table II. ANF concentrations before and after intravenous volume infusion

	0 min	*5 min*	*10 min*	*15 min*	*20 min*	*30 min*
Pregnant ($n = 8$)	78.62 ± 4.82	89.48 ± 5.60	83.79 ± 6.21	80.14 ± 3.29*	81.25 ± 3.63*	82.44 ± 2.65*
Nonpregnant ($n = 5$)	88.45 ± 11.77	91.55 ± 9.39	101.93 ± 9.49	116.15 ± 3.66	121.99 ± 11.95†	134.11 ± 12.92†

*$p < 0.001$ between pregnant and nonpregnant patients at each time point.
†$p < 0.05$ between time 0 and 20, 30, 40, and 50 minutes for nonpregnant subjects only.

Table III. Serum osmolality before and after intravenous volume infusion

	Osmolality (mOsm/kg)		
	0 min	*20 min*	*50 min*
Pregnant	274.39 ± 2.15 ($n = 7$)	279.20 ± 4.27 ($n = 7$)	279.57 ± 4.56 ($n = 6$)
Nonpregnant	273.75 ± 7.27 ($n = 4$)	269.80 ± 4.74 ($n = 4$)	280.28 ± 7.41 ($n = 4$)

Values are mean ± SEM.

Table IV. Hematocrit levels before and after intravenous volume infusion

	Hematocrit (%)		
	*0 min**	*20 min**	*50 min**
Pregnant	33.37 ± 1.27 ($n = 8$)	30.00 ± 1.51 ($n = 8$)	30.43 ± 0.95 ($n = 7$)
Nonpregnant	36.50 ± 3.12 ($n = 4$)	34.00 ± 2.43 ($n = 5$)	36.40 ± 2.38 ($n = 5$)

Values are mean ± SEM.
*$p = 0.01$ by analysis of variance, repeated measures test, and Newman-Keuls test. Values at 20 and 50 minutes are less than those at time 0.

Table V. Mean arterial blood pressure before and after intravenous volume infusion

	Mean arterial pressure (torr)		
	0 min	*20 min*	*50 min*
Pregnant ($n = 8$)	80.38 ± 4.08	83.63 ± 2.95	80.00 ± 4.80
Nonpregnant ($n = 5$)	84.40 ± 3.83	89.00 ± 1.30	90.80 ± 3.75

Values are mean ± SEM.

Table VI. Heart rate before and after intravenous volume infusion

	Heart rate (beats/min)		
	0 min	*20 min**	*50 min**
Pregnant ($n = 8$)	86.30 ± 6.10	93.00 ± 4.21	103.00 ± 8.10
Nonpregnant ($n = 5$)	67.00 ± 7.18	69.40 ± 3.68	60.40 ± 4.78

Values are mean ± SEM.
*$p = 0.001$ between pregnant and nonpregnant subjects.

or short-term volume expansion affect circulating maternal ANF levels? We have previously reported that long-term volume expansion that occurs during normal human pregnancy does not appreciably change maternal ANF levels.[3] We present data on the changes in ANF levels after acute volume expansion at term.

This is the first instance where the response in ANF concentrations to an acute volume stimulus was studied

40 min	*50 min*
88.05 ± 5.83	87.37 ± 6.48
(n = 7)	(n = 6)
138.18 ± 14.07†	144.69 ± 8.67†

in pregnant women at term and was compared with that seen in nonpregnant subjects. We selected patients who were to undergo an elective cesarean section at term while under conduction anesthesia for several reasons. These patients were not in labor and had no complications. They *would have* normally received a volume stimulus, of the magnitude described in the Material and methods section, in the routine course of preanesthesia volume expansion. Thus our study presented *minimal* risk to the patients and their fetuses. Although we did contemplate the measurement of intravascular volume in these subjects, our institutional review board felt that the benefits did not outweigh the potential risks. As a result no intravascular volume studies were performed. Thus volume infusion was based on estimates derived from the subjects' body weights. We did not use a Foley catheter to evaluate urine and electrolyte outputs because the question this study was designed to answer was limited to the effects of an exogenous intravenous fluid bolus on venous ANF concentrations. Moreover, the institutional review board felt that for the nonpregnant subjects a Foley catheter might have represented more than minimal risk.

The major part of volume expansion took place during the first 20 minutes of the study period, during which time the epidural anesthetic had not been injected. After 25 minutes local anesthetic was injected in the epidural catheter, and an adequate level of anesthesia was achieved by 50 to 60 minutes from the start of the infusion (one patient received a spinal anesthetic). Nonpregnant subjects did not undergo conduction anesthesia. We have found that nonpregnant women showed a significant increase in ANF levels as early as 20 minutes after the start of the fluid infusion. In contrast, pregnant women did not show an appreciable increase in ANF concentrations. Thus, during the time that the local anesthetic had not been injected (<20 minutes), ANF levels did not increase in pregnant women, but they did increase significantly in the nonpregnant group. However, beyond the 25-minute point, the lack of ANF response in the pregnant group might be partially accounted for by the vasodilation occurring in association with the epidural anesthetic. The latter would have resulted in intravascular space expansion and could conceivably have blunted the response.

Given these considerations, our observations suggest that circulating maternal plasma ANF concentrations do not increase as a result of a substantial *short-term* volume load. This response is different from that seen in nonpregnant human subjects or in pregnant ewes.[10] Finally, we have confirmed our previous observations that there is no difference between maternal ANF concentrations during pregnancy and those seen in nonpregnant subjects.[3]

No significant changes in serum osmolality were noted at the three time points we had selected as our sampling points. This rules out any potential effects of changes in serum osmolality on ANF secretion. In contrast, hematocrit levels did decrease, albeit very modestly. The latter is consistent with intravascular dilution.

Although mean arterial blood pressure did not change as a result of the infusion, interestingly, maternal heart rate increased at 20 minutes and increased further at 50 minutes after the start of the infusion. This observed increase apparently did not have any impact on maternal ANF concentrations. It has been reported that marked ventricular tachycardia might stimulate ANF secretion.[11]

From this study of acute volume expansion we conclude that in normal pregnancy an intravascular volume increase may not be sensed adequately by atrial volume sensors. This is in contrast to nonpregnant women who did show a significant increase in circulating ANF levels as a response to a comparable intravenous volume stimulus. This lack of response in circulating ANF concentrations in pregnant women to a significant intravenous volume stimulus could be due to an enlarged maternal vascular compartment during pregnancy. The latter might have prevented a significant increase in intraatrial pressure and volume. Noninvasive or invasive hemodynamic studies might have to be carried out to provide a partial answer to that question. Finally, increased ANF clearance might be partially responsible for this lack of response during pregnancy. Further studies will be necessary to determine the contribution of these potential variables.

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In utero detection of cardiac failure from an aneurysm of the vein of Galen

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The detection of a vein of Galen aneurysm in a hydrocephalic fetus is presented. The differential diagnosis for the midline cystic structure was made on the basis of the presence of high-velocity flow on Doppler ultrasonographic examination. (Am J Obstet Gynecol 1990;163:50-1.)

Key words: Abnormalities, multiple diagnosis, prenatal diagnosis, ultrasonographic diagnosis, vein of Galen aneurysm

The vein of Galen aneurysm is the generic name for midline arteriovenous fistula malformations associated with aneurysmal dilatation of the vein of Galen.[1] The common clinical features in the neonate are cardiomegaly with congestive heart failure and increased intracranial pressure with hydrocephaly or cranial bruit. When the associated intracranial abnormality is not recognized, unnecessary cardiac examinations are performed that delay the diagnosis and treatment. Because the diagnosis of the fetal-neonatal form is almost pathognomonic, we present a case that illustrates the pertinent findings.

Case report

A 24-year-old gravida 2, para 1-0-0-1 patient was referred to us because an examination performed by her obstetrician revealed hydrocephalus. On examination there was no dilatation of the ventricular system, but a midline cystic structure was present that extended posteriorly in the direction of the straight sinus (Fig. 1). Marked enlargement of the vessels of the polygon of Willis, sigmoid sinus, common carotid arteries, jugular veins, superior vena cava, and main pulmonary artery and ductus was noted. The heart was remarkable for the enlargement of the right cavities, as compared with the left. The foramen flap bulged in the left atrium without the usual flapping. The newborn was born at term. He was treated with embolization of the fistula by coils[2] that were complicated by intracranial hemorrhages and seizures. He died of cardiac failure at 6 months of age.

Comment

Asymmetry of the cardiac chambers is an unusual finding in utero. In this case the large excess flow exceeded the capacity of the natural right-to-left shunts. The classic appearance of the varix is of a midline hypoechoic structure. The denomination of aneurysm of the vein of Galen includes different arteriovenous fistulae located in the vicinity of the midbrain that vary from a single large aneurysmal dilatation of the vein

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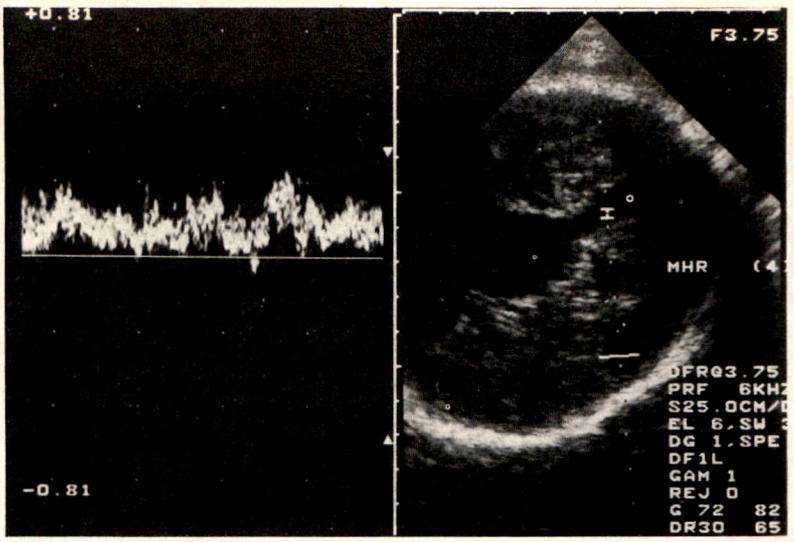


Fig. 1. Doppler ultrasonography and two-dimensional examination of the aneurysmal dilatation of the vein of Galen. Volume sample is placed in draining vessel that exhibits a large amount of low-resistance turbulent flow.

of Galen to multiple communications between the vein and the carotid and vertebrobasilar systems. The most common types are the arteriovenous fistula of the vein of Galen, a cerebral arteriovenous malformation with ectasia of the vein of Galen, or a varix of the vein of Galen. Aside from congestive heart failure, the shunt can also create hydrocephalus by compression of the aqueducts, a steal phenomenon that is responsible for parenchymal loss or atrophy, and decrease or absence of short- and long-term heart variability because of cerebral hypoxia. Pineal malformation may also result from the compression and the steal phenomenon.

There are very few anomalies that can appear as a midline cystic structure. The most likely, of course, is an arachnoid cyst. Far less likely diagnoses include coloid cysts, choroid plexus cysts, porencephalic cysts, pineal tumors, intracerebral hematoma, and choroid papilloma. What is unique in the vein of Galen aneurysm is the presence of high-velocity flow on the Doppler examination. None of the other differential diagnoses should present any such flow. The recognition of cardiomegaly (especially at the expense of the right side) and the detection of the massively distended jugular vein establish the diagnosis.

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Morphologic study of changes of collagenous tissue in the amnion and cervix during prostaglandin-induced abortion and delivery

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Marked dissociation of the cervical collagenous tissue during prostaglandin-induced abortion is well recognized, but the response of collagenous tissue of the amnion to prostaglandin treatment is not known. A morphologic study of amniotic collagenous tissue was performed after prostaglandin-induced abortion and prostaglandin-induced term delivery. The collagenous fibers of the amnion were found to be closely packed with no ground substances and formed in a thick layer. Cervical collagenous tissue of the same patients showed a marked dissociation of fibers and abundant ground substance. The fetus was often delivered within a complete sac at midtrimester. These findings suggest differences in collagenous tissue responses to prostaglandin treatment between the amnion and cervix. (Am J Obstet Gynecol 1990;163:52-6.)

Key words: Collagenous tissue, amnion, cervix, prostaglandins

Prostaglandins (PGs) delivered by various routes can ripen the cervix either in the nonpregnant state or during pregnancy. The histologic appearance of the cervix in PG-induced abortion shows the changes found in the cervix at term. The collagenous tissue shows marked dissociation of fibers and the amount of ground substance is increased.[1, 2]

The amniotic membrane also consists of collagenous connective tissue. Although the collagenous tissue of the amnion is extremely thin,[3] it plays an important role in the resistance of the amnion to premature rupture during normal pregnancy.[4] Our morphologic study showed that collagenous tissue in the human amnion, in contrast to that in the cervix, was not dissociated and had no ground substance when examined during normal pregnancy and delivery.[3]

In PG-induced abortion we often find that, despite marked cervical softening and nonphysiologically strong uterine contractions, the fetus is delivered within a complete sac. This is also noted in pure stretch-induced abortion,[3] and there is no marked difference between the two.

In this study we morphologically compared collagenous tissue and fibroblasts of the amnion with those of the cervix after PG-induced abortion and delivery.

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Material and methods

Samples of the amnion and cervix were collected from 24 normal women at different stages of pregnancy: during midtrimester between 13 and 16 weeks ($n = 8$), between 17 and 21 weeks ($n = 8$), and at the end of pregnancy between 38 and 41 weeks' gestation ($n = 8$). None of the patients had any evidence of infection, judging from body temperature and plasma levels of C-reactive protein. No limitations were placed on the age or parity of the patients.[3] The purpose and nature of the study were explained to each patient and their written consent was obtained.

For abortion at midtrimester, vaginal suppositories that contained 1 mg of a PGE_1 analog (Pregrandin, Ono Pharmaceutical Co., Japan) were inserted into the posterior fornix.[5] For the induction of labor at term, the intravenous infusion of a PGF analog (Prostarmon-F, Ono Pharmaceutical) was used.

Immediately after placental delivery, discs of fresh amniotic membrane were excised from the placental and reflected regions. They were processed as described previously[3] for light and electron microscopic examination. Cervical samples were obtained from the same patients. Small wedge-shaped biopsy specimens were taken from two points: (1) approximately 1 cm from the squamocolumnar junction and (2) from the glandular region.

The biopsy specimens for morphologic study were

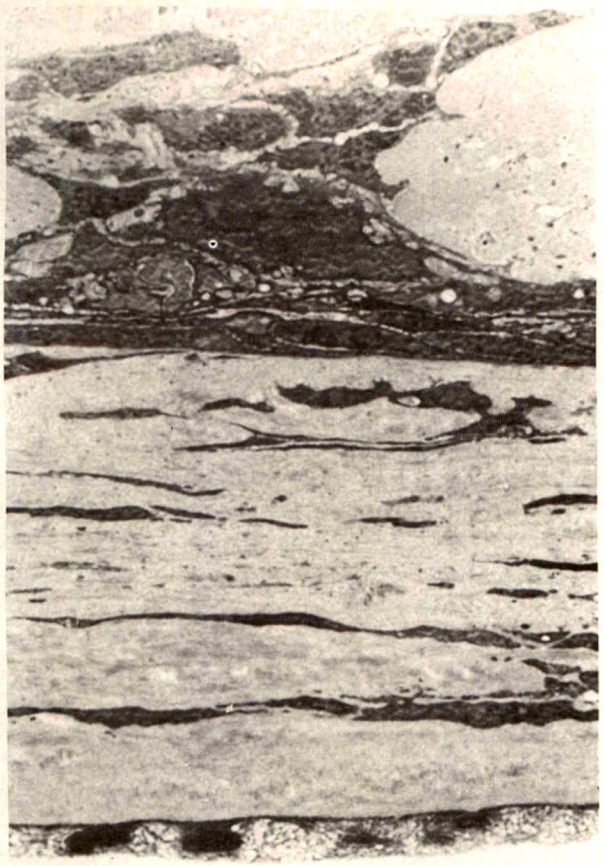


Fig. 1. Amnion from patient with prostaglandin-induced abortion (21 weeks' gestation). From top to bottom, epithelium, collagenous tissue, in which fibroblasts are intermingled, and trophoblastic layer are observed. Collagenous fibers are compact and densely packed. No leukocyte infiltration is observed. (Sections from material embedded in Epon plastic, stained with toluidine blue. Original magnification ×600.)

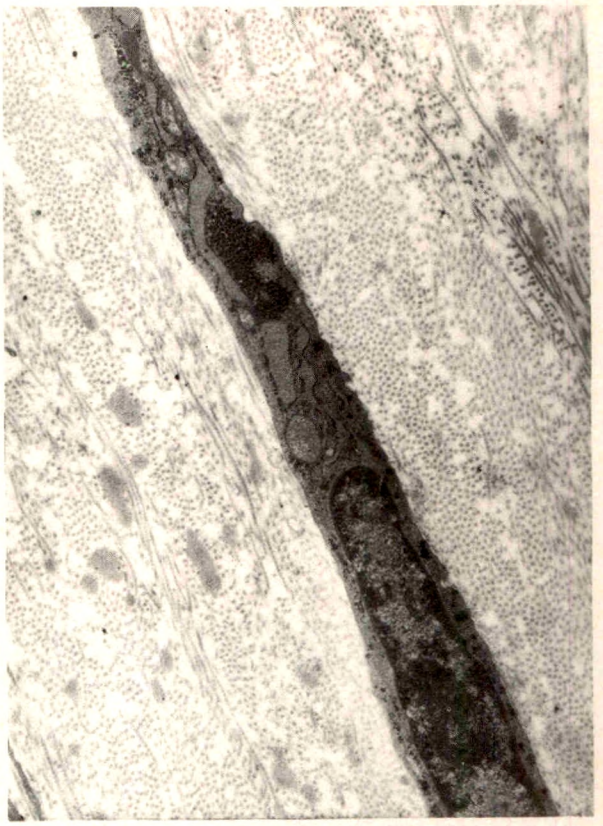


Fig. 2. Electron micrograph of fibroblast layer of amnion from same patient as shown in Fig. 1. Collagen fibrils are regularly oriented and compact. Amorphous ground substance is not noted. Fibroblast shows massive accumulation of glycogen granules and few vesicles located close to plasma membrane. In this case fetus was delivered within unruptured sac. (Original magnification ×11,800.)

immediately fixed with 2% paraformaldehyde in 0.1 mol/L sodium cacodylate buffer (pH 7.4) with 0.25 mol/L sucrose at 0° C to 4° C for 12 hours. After fixation the specimens were embedded in paraffin, sectioned, and stained by the hematoxylin-eosin, Gomori trichrome, and Sudan III methods.

The other specimens were fixed with 2% glutaraldehyde in 0.1 mol/L cacodylate buffer (pH 7.4) with 0.25 mol/L sucrose at 0° C to 4° C for 3 hours. The subsequent processing was as has been previously described.[3] Ultrathin sections were observed under a Hitachi H-500 electron microscope. Also sections 1 μm thick from specimens embedded in Epon plastic for the electron microscopic study were stained with toluidine blue and observed under a light microscope.

The thickness of the amnion was determined by light microscopy of vertical sections.

Results

Fig. 1 shows a light micrograph of the amnion obtained after prostaglandin-induced abortion at 21 weeks' gestation. The amnion under the epithelium had a more homogenous and compact collagen layer than that of the cervix, regardless of the stage at which the sample was obtained. The amorphous ground substance was absent. The thickness of the amnion ranged from 0.08 to 0.12 mm and did not vary significantly among the specimens. No leukocyte infiltration was noted in any of the specimens.

Fig. 2 shows an electron micrograph of connective tissue in the amnion from the same patient as shown in Fig. 1. The collagenous tissue was dense and composed of a vast number of collagen fibers embedded in a matrix of low density. Fine granular or amorphous ground substance was not seen. Ultrastructurally, fi-

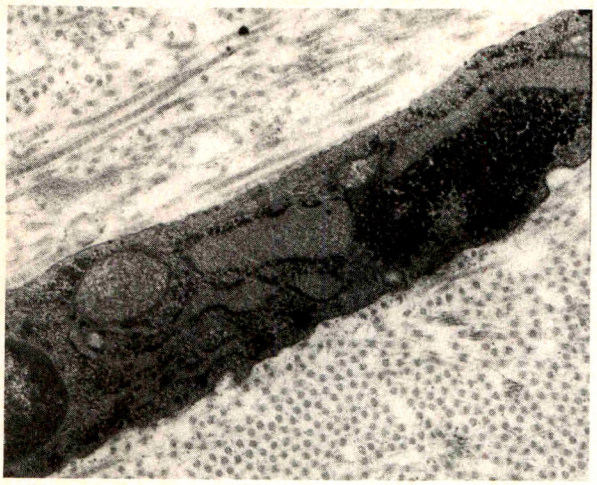


Fig. 3. Higher magnification of fibroblast shown in Fig. 2. Marked glycogen deposition and few pinocytotic vesicles are visible. (Original magnification ×23,000.)



Fig. 4. Cervix from same patient as shown in Fig. 1. Collagen fibers are markedly dissociated, and edema and ground substances are increased compared with those of amnion. No leukocyte infiltration is observed. Specimen was taken 1 cm from squamocolumnar junction. (Section from material embedded in Epon plastic, stained with toluidine blue. Original magnification ×600.)

broblasts contained marked glycogen deposition and occasional pinocytotic vesicles; these findings were similar in all specimens studied (Fig. 3).

At a higher magnification (Fig. 3), the amnion exhibited regularly oriented and closely interwoven collagen fibrils, about 50 nm in diameter. The fibrils showed a periodicity of approximately 60 nm, which is typical for collagen. The densely packed collagen fibrils showed no sign of splitting or dispersion, and the absence of amorphous ground substance was characteristic. The compact arrangement of the collagen fibrils did not vary with the stage of pregnancy.

Light microscopy of the cervix (Fig. 4) revealed marked edema in all specimens, as evidenced by the many clear spaces observed between individual collagen fibers. The collagen fibers were clearly more dispersed and the ground substance was markedly increased compared with those of the amnion. Increased vascularity and the presence of dilated blood vessels were noted regardless of the site of biopsy. Leukocyte infiltration was not observed when the specimen was taken 1 cm from the squamocolumnar junction but leukocyte infiltration was noted in specimens taken from the glandular region (i.e., inside the squamocolumnar junction).

The electron microscopic appearance of the cervix markedly differed from that of the amnion. During pregnancy (Fig. 5) and at term the collagen fibers (i.e. the bundles of fibrils) were sparse and less regularly oriented than those in the amnion. Abundant deposits of amorphous ground substance were commonly present between the fibers. Ultrastructurally, the fibroblasts, in comparison with those in the amnion, contained fewer glycogen granules and a markedly larger number of vesicles close to the plasma membrane and of invaginations of the membrane (Fig. 6). The findings were similar in all specimens.

At a higher magnification (Fig. 6), the dispersion at the collagen fibers was more clearly visible. The gaps between the fibers were increased, although the fibrils still had periodic bands of approximately 60 nm as in the case of the amnion. Amorphous ground substance around the collagen fibers and fibrils was far more abundant than that in the amnion. The same dispersed collagen arrangement and abundance of ground substance were noted in all specimens.

During PG-induced abortion at midtrimester (13 to 22 weeks' gestation), of a total of 16 patients there were 11 fetal deliveries with unruptured sacs or with rupture of the membranes protruding out of the vagina. In the majority of term patients, rupture of the membranes usually occurred when the cervix was more widely dilated than on abortion at midtrimester.

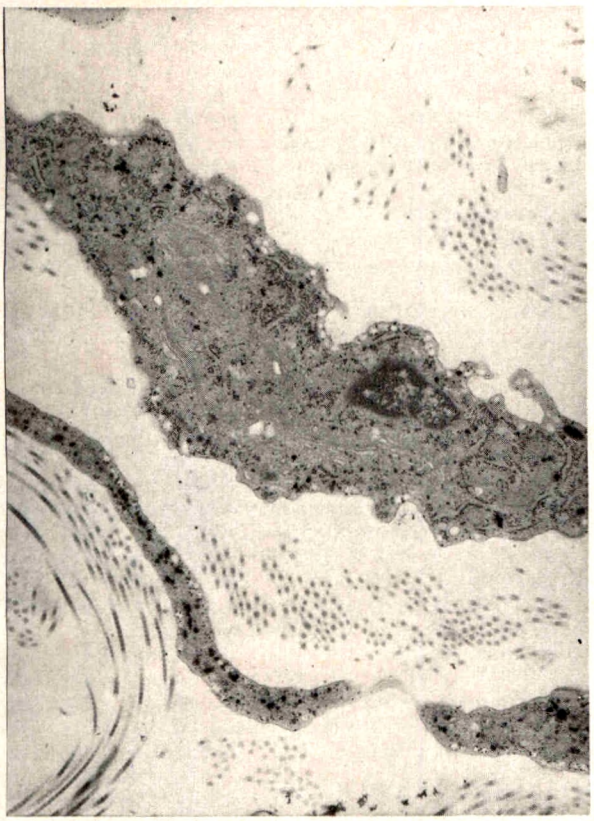


Fig. 5. Electron micrograph of cervix from same patient as shown in Fig. 1. Collagenous fibers are dissociated and abundant amorphous ground substance is present, which appears as dark areas in photograph. Fibroblast has many vesicles located close to plasma membrane, and few glycogen granules are seen. (Original magnification ×11,800.)

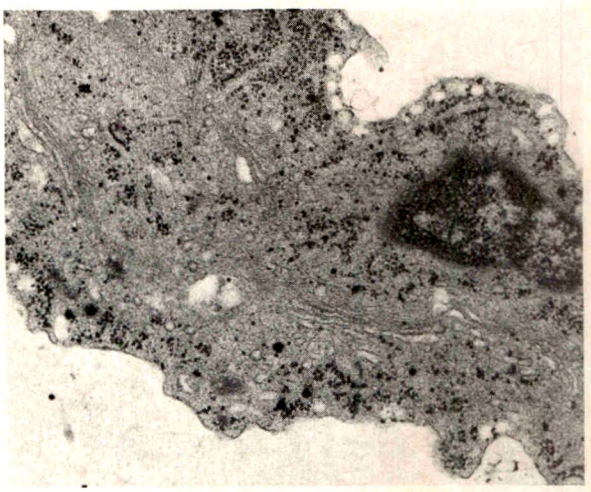


Fig. 6. Higher magnification of fibroblast shown in Fig. 5. Many vesicles close to plasma membrane and few glycogen granules are observed. (Original magnification ×23,000.)

Comment

The present findings histologically showed that the response to PG treatment of collagenous tissue in the amnion is different from that in the cervix. In PG-induced cervical ripening, tissue collagenase levels increase[6] or are unchanged.[7] The amount of tissue collagen is unchanged[1] or decreases.[8] A significant increase in the concentration of sulfated glycosaminoglycans has been noted in the cervix after PG treatment.[1] PGs have been shown to stimulate synthesis of proteoglycans in cultured fibroblasts[9] and in the human uterine cervix under in vitro conditions.[10] The increase of the amorphous substance between collagenous fibers in the PG-treated [1,2] and intrapartum cervix[11] is thought to be assoicated with the newly synthesized proteoglycans.

The present findings showed that the amniotic collagen apparently resisted tissue dissociation and weakening in PG-induced abortion. Both histologic evidence and the clinical findings that the fetus often was delivered within an intact sac despite strong uterine contractions support this conclusion. Because no ground substance was noted among the collagen fibers, PGs do not appear to activate fibroblasts in the amnion to synthesize ground substances (i.e., proteoglycans). Also, because there was no dissociation of collagen fibers, the amniotic collagenous tissue appeared not to contain active collagenase. Biochemical studies to clarify these points are in progress. The resistance of the amnion to tissue decomposition by exogenous PGs is in agreement with the same property of the tissue noted during stretch-induced abortion and at normal term delivery[5]; endogenous PG production is known to increase on the former[12] and latter occasions.

Differences in the fibroblasts from the amnion and the cervix were noted. Cervical but not amniotic fibroblasts seemed to be activated as shown by the large number of cytoplasmic vesicles (pinocytotic vesicles) located close to the cell membrane, as has been previously noted by others.[1,2] Fibroblasts in the amnion and cervix seemed to have different characteristics. We found that glycogen granules increase in many fetal cells in a similar manner to those in the amniotic fibroblasts, but the implications of this phenomenon are not clear.

The reason for the different characteristics of collagenous tissue in the amnion and cervix is not clear, but it could be because of the different embryologic origins of these tissues. Collagenous tissue in the amnion is derived from the extraembryonic somatopleuric mesoderm and that in the cervix is of intraembryonic origin.

There has been discussion of the role of leukocyte

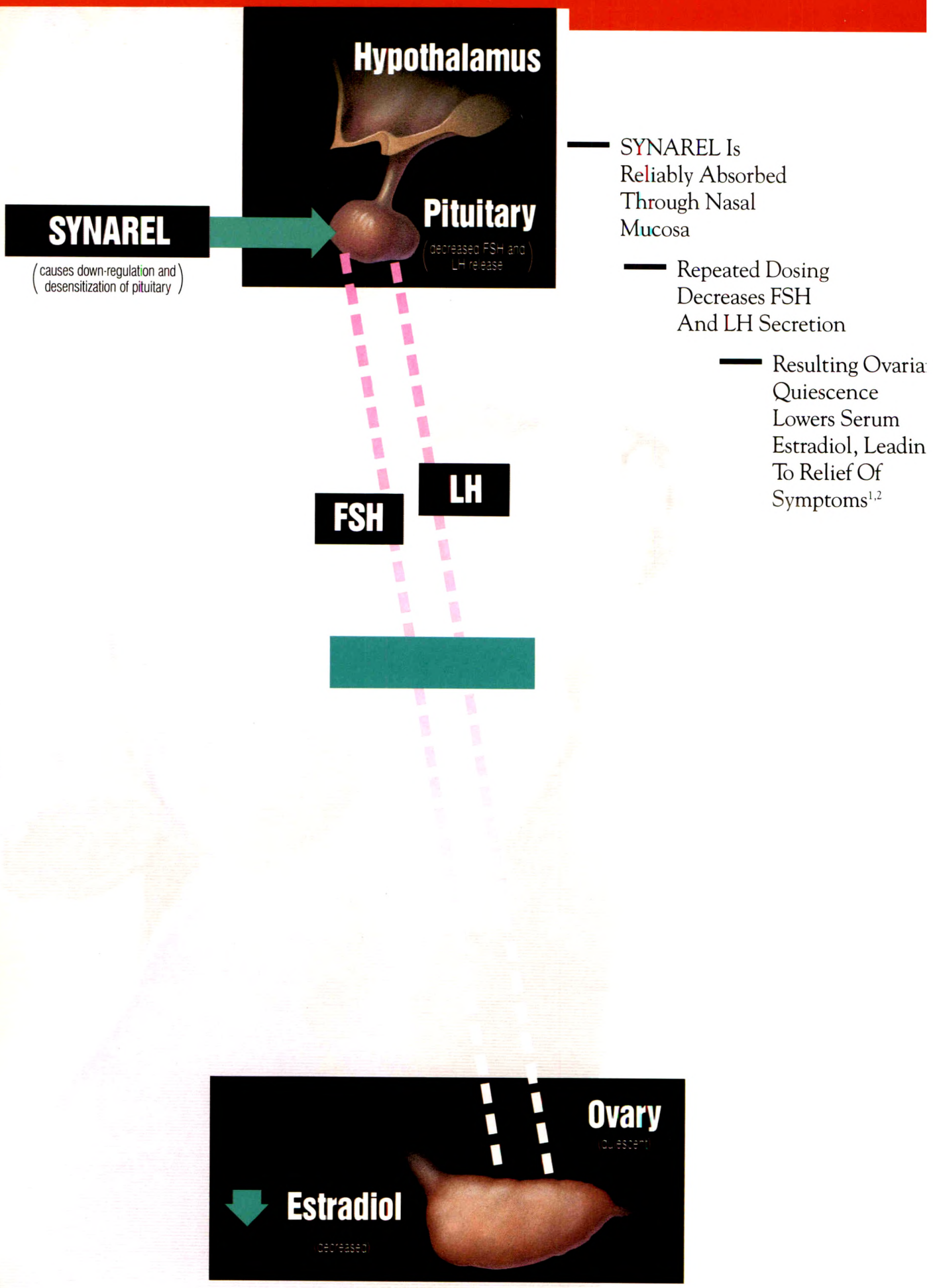
factors in the softening of the cervix.[11] We have reported that intrapartum leukocyte infiltration in the cervix is localized to the glandular region in normal pregnancy, whereas the major part of the cervix covered by squamous epithelium[3] and the vagina[13] remain without leukocyte infiltration. Previous analysis of cervical collagenous tissue by other investigators has not shown evidence of leukocyte infiltration caused by PG treatment,[2,7] and our present findings coincide with the previous reports. In the amnion, marked leukocyte infiltration was not noted in stretch-induced and normal term delivery,[3] similar to the present results for PG treatment.

There has been a great deal of discussion of the role of perinatal infections as an etiologic factor in the preterm rupture of the membranes and preterm labor.[14] Extrapolation of these abnormal conditions to normal uninfected term delivery is difficult according to our research.[3] It is also difficult to associate premature rupture of the membranes with increased intrinsic PG elaboration by leukocytes because the collagenous tissue of the amnion resists PG treatment. Nevertheless, neutrophils are a well known source of collagenase[15] and PGs.[16] A light and electron microscopic study is in progress on collagenous tissue of the amnion and cervix in cases of severe infection.

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Endometriosis
Therapy
Breakthrough
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Hypothalamus
Pituitary
(decreased FSH and LH release)
SYNAREL
(causes down-regulation and desensitization of pituitary)
SYNAREL Is Reliably Absorbed Through Nasal Mucosa
Repeated Dosing Decreases FSH And LH Secretion
Resulting Ovaria Quiescence Lowers Serum Estradiol, Leadin To Relief Of Symptoms[1,2]
LH
FSH
Ovary
Estradiol

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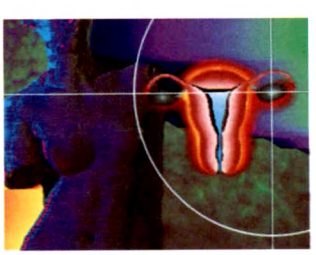
— **94% Of Synarel Patients Reported Improvement Of Symptoms**

— **86% Of Patients Showed Improvement Of Endometriotic Lesions**

— **Lowers Estrogen Without Adding Androgens**[1,2]

— **Significantly Fewer Masculinizing Side Effects Than Danazol** (The most frequent side effects are those associated with hypoestrogenism)

— **The Only GnRH Agonist Administered Intranasally**



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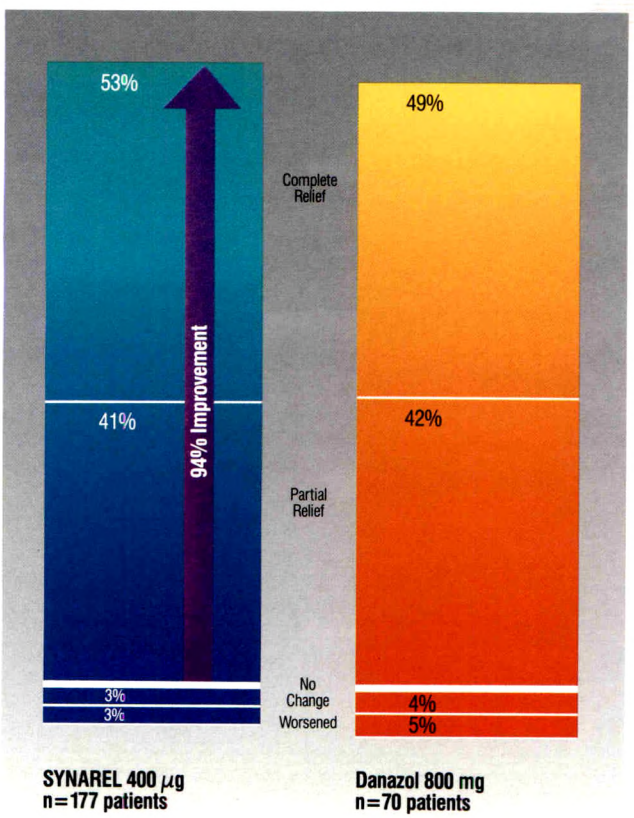
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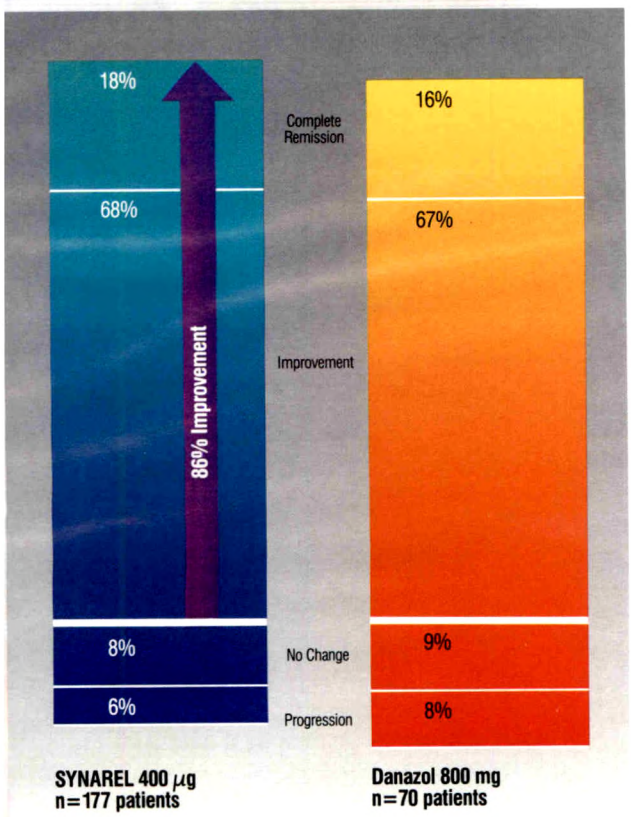
94% Of Synarel Patients Reported Improvement Of Symptoms



Changes in symptom severity scores from admission to end of study

- Relieves dysmenorrhea, dyspareunia and pelvic pain
- Sustained efficacy in 83% of patients 6 months post-treatment

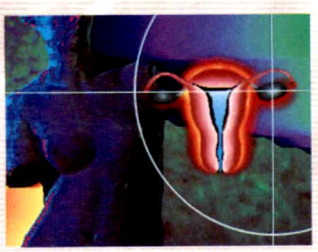
86% Of Patients Showed Improvement Of Endometriotic Lesions



Changes in laparoscopy scores from admission to end of therapy

- Post-therapy laparoscopy confirmed improvement in all stages† of endometriosis
- Number of patients in Stages III and IV decreased 42% and 57% respectively
- Retreatment cannot be recommended since safety data for retreatment are not available

†Based on American Fertility Society laparoscopy score stages: 0 (absent, score 0), I (minimal, 1–5), II (mild, 6–15), III (moderate, 16–40), IV (severe, >40).



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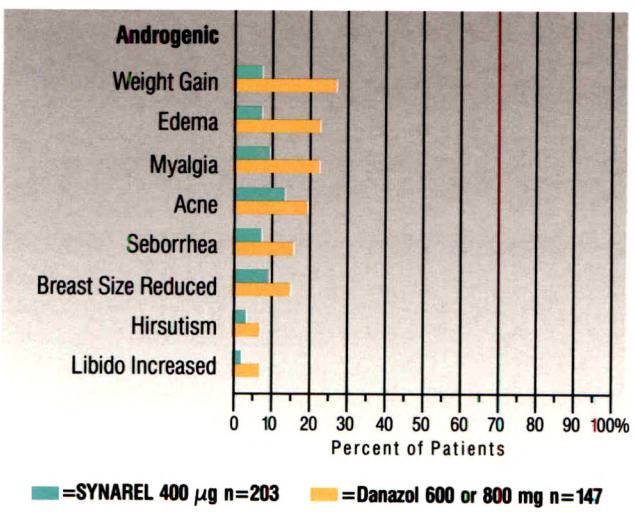
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Lowers Estrogen Without Adding Androgens[1, 2]

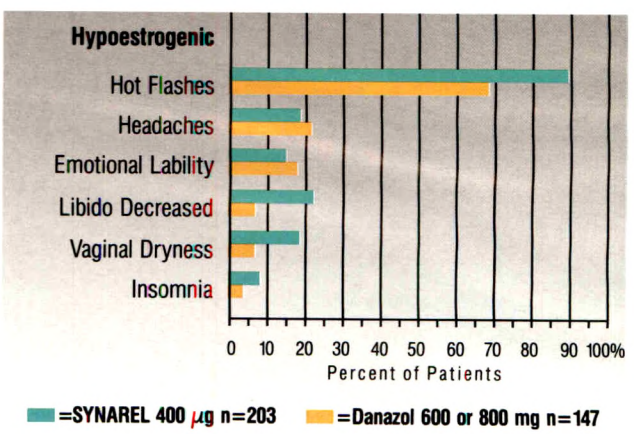
Synarel Exhibits Fewer Masculinizing Side Effects Than Danazol



Adverse events during 6 months treatment

- More frequent and/or severe with danazol:
  Weight gain
  Edema
  Acne
  Oily skin
  Hirsutism
- Some androgenic effects of danazol—such as voice deepening—may be irreversible[3]
- Patients should be advised to use non-hormonal methods of contraception when taking SYNAREL

Synarel Exhibits Predictable Hypoestrogenic Profile



Adverse events during 6 months treatment

- Estrogen levels return to normal after cessation of therapy
- Bone changes largely reversible 6 months post-treatment

Bone Density Changes During And After Treatment With SYNAREL (400 μg/day)

Site Method Units	Time of Study Baseline	End of Treatment	Post-treatment
Lumbar Vertebrae QCT,* Integral (g/vertebrae) n=21	13.4	12.8 −4.3%	13.1 −3.3%
Trabecular Bone of Vertebrae QCT* (mg/cc) n=23	161.3	147.6 −8.7%	152.0 −4.9%
Lumbar Vertebrae DPA† (g/cm^2) n=6	0.98	0.93 −5.9%	0.96 −1.4%
Distal Radius SPA** (Units) n=6	40.2	39.5 −1.6%	39.6 −0.8%

Percent changes from baseline

*Quantitative computed tomography
†Dual photon absorptiometry
**Single photon absorptiometry

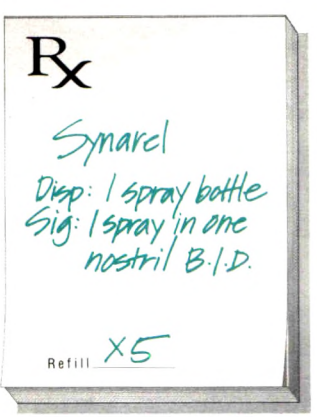
Intranasal Administration

Synarel Is The Only GnRH* Agonist Administered Intranasally

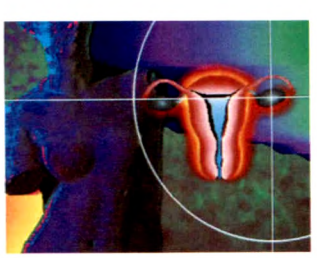


B.I.D. controlled-dose administration offers:

- Highly accurate metered-dose delivery—200 µg/spray
- Reliable absorption through nasal mucosa
- Patient convenience with low incidence of nasal irritation (10%)



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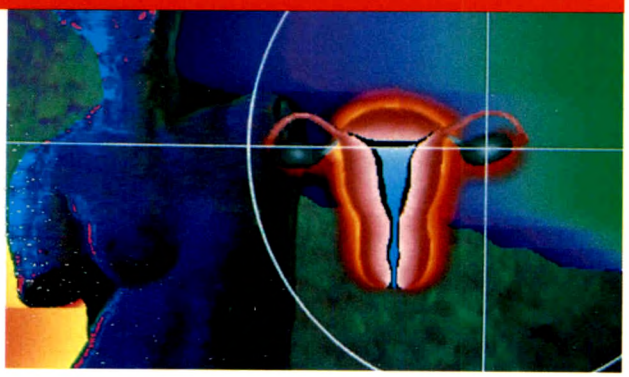
NASAL SOLUTION, 2 MG/ML

*Gonadotropin-Releasing Hormone Analog

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New SYNAREL® For Endometriosis

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— **The Only GnRH* Agonist Indicated For The Management Of Endometriosis**

— **Unsurpassed Resolution Of Pain And Endometriotic Lesions**

— **Fewer Masculinizing Side Effects Than Danazol** (The most frequent side effects are those associated with hypoestrogenism)

— **The Only GnRH Agonist Administered Intranasally**

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*Gonadotropin-Releasing Hormone Analog

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829-G2-108-89

SYNTEX

SYNTEX LABORATORIES, INC.
PALO ALTO, CA 94304

BRIEF SUMMARY

SYNAREL® Nasal Solution contains nafarelin acetate (2 mg/mL, expressed as nafarelin base), benzalkonium chloric glacial acetic acid, sodium hydroxide or hydrochloric acid, sorbitol, and purified water.

INDICATIONS AND USAGE: For management of endometriosis. Experience is limited to women 18 years and old treated for 6 months.

CONTRAINDICATIONS: Hypersensitivity to GnRH, GnRH agonist analogs or any excipients in SYNAREL; undia nosed abnormal vaginal bleeding; pregnancy or possibility of pregnancy while taking the drug because SYNAREL ma cause fetal harm when administered to a pregnant woman. If SYNAREL is used during pregnancy or if the patie becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus; use in women wh are breast feeding.

WARNINGS: Safe use in pregnancy has not been established clinically. Before starting treatment pre nancy must be excluded.

When used regularly at the recommended dose, SYNAREL usually inhibits ovulation and stops menstruation. Conti ception is not insured, particularly if patients miss successive doses. Therefore, patients should use nonhormonal cc traception. Advise patients to see their physician if they believe they may be pregnant. If a patient becomes pregnai during treatment, discontinue the drug; apprise patient of the potential risk to the fetus.

PRECAUTIONS Information for Patients: 1. Since menstruation should stop with SYNAREL, the patient shoul notify her physician if regular menstruation persists. Patients missing successive doses may experience breakthroug bleeding.

2. Patients should not use SYNAREL if pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or ar allergic to any of its ingredients.

3. Safe use in pregnancy has not been established. Therefore, a nonhormonal method of contraception should b used during treatment. If a patient becomes pregnant during treatment, she should discontinue the drug and consu her physician.

4. Adverse events occurring most frequently in clinical studies are associated with hypoestrogenism. Nasal irritatio occurred in about 10% of patients.

5. Induced hypoestrogenic state results in a small loss in bone density over a 6-month treatment course. Some of thi loss may not be reversible. During one six-month treatment period, this should not be important. In patients with majc risk factors for decreased bone mineral content, i.e., chronic alcohol and/or tobacco use, strong family history c osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, SYNARE may pose additional risk. In these patients risks and benefits must be weighed carefully. Repeated courses of treatmer with GnRH analogs are not advisable in patients with major risk factors for loss of bone mineral content.

6. Patients with intercurrent rhinitis should consult their physician for use of a topical nasal decongestant. If a topica nasal decongestant is required during treatment, it must be used at least 30 minutes after SYNAREL dosing to decreas the possibility of reducing drug absorption.

7. Retreatment cannot be recommended since safety data beyond 6 months are not available.

Drug Interactions: No pharmacokinetic-based drug-drug interaction studies have been conducted. Nafarelin acetat is a peptide primarily degraded by peptidase and not by cytochrome P-450 enzymes, and is only about 80% bound t plasma proteins at 4°C; therefore drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions: SYNAREL in therapeutic doses suppresses the pituitary-gonadal system. No mal function is usually restored 4–8 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitar gonadotropic and gonadal functions during treatment and up to 4–8 weeks after discontinuation of SYNAREL may b misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in rats an mice at intramuscular doses up to 110 times and 560 times the maximum recommended human intranasal dos respectively. These multiples of the human dose are based on the relative bioavailability of the drug by the two routes o administration. As with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonge periods induced hyperplasia and/or neoplasia of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treatec groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive tc hormonal stimulation.

Mutagenicity studies using bacterial, yeast, and mammalian systems provided no evidence of mutagenic potentia

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when treatment was discontinued after continuous administration for up to 6 months.

Pregnancy, Teratogenic Effects: *Pregnancy Category X.* Intramuscular SYNAREL was administered to rats throughout gestation at about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration. An increase in major fetal abnormalities was seen in 4/80 fetuses at the highest dose. A similar study at the same doses in rats and studies in mice and rabbits at doses up to 600 μg/kg/day and 0.18 μg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration throughout gestation. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers: It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined SYNAREL should not be used by nursing mothers.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most frequently reported adverse reactions were those related to hypoestrogenism. In controlled studies comparing SYNAREL (400 μg/day) and danazol (600 or 800 mg/day), the following adverse reac tions were most frequently reported and thought to be drug-related.

Hypoestrogenic: hot flashes (SYNAREL 90%, danazol 69%), decreased libido (22%, 7%), vaginal dryness (19% 7%), headaches (19%, 21%), emotional lability (15%, 18%), insomnia (8%, 4%); **Androgenic:** acne (13%, 20%), myalgia (10%, 23%), reduced breast size (10%, 16%), edema (8%, 23%), seborrhea (8%, 17%), weight gain (8%, 28%), hirsutism (2%, 6%), increased libido (1%, 6%); **Local:** nasal irritation (10%, 3%); **Miscellaneous:** depression (2%, 5%), weight loss (1%, 3%).

Less than 1% of patients experienced paresthesia, palpitations, chloasma, maculopapular rash, eye pain, urticaria, asthenia, lactation, breast engorgement, and arthralgia. In clinical trials, immediate hypersensitivity thought to be pos sibly or probably related to nafarelin occurred in 3 (0.2%) of 1509 healthy subjects or patients.

Changes in Bone Density: After 6 months' treatment vertebral trabecular bone density and total vertebral bone mass, measured by quantitative computed tomography (QCT), decreased by an average of 8.7% and 4.3%, respectively, com pared to pretreatment levels. There was partial recovery of bone density post-treatment; the average trabecular bone density and total bone mass were 4.9% and 3.3% less than pretreatment levels, respectively. Total vertebral bone mass, measured by dual photon absorptiometry (DPA), decreased by a mean of 5.9% at end of treatment. Mean total vertebral mass, re-examined by DPA 6 months post-treatment, was 1.4% below pretreatment levels. There was little, if any, decrease in the mineral content in compact bone of the distal radius and second metacarpal. Use for longer than the recommended 6 months or in presence of other known risk factors for decreased bone mineral content may cause addi tional bone loss.

Changes in Laboratory Values: *Plasma enzymes.* During clinical trials SGOT and SGPT levels were more than twice the upper limit of normal in only one patient each. There was no other evidence of abnormal liver function and levels returned to normal after treatment was stopped.

Lipids. At enrollment and at end of treatment, 9% of patients on SYNAREL 400 μg/day and 2% on danazol had total cholesterol values above 250 mg/dL.

Of those with pretreatment cholesterol values below 250 mg/dL, 6% on SYNAREL and 18% on danazol had post treatment values above 250 mg/dL.

Mean (±SEM) pretreatment values for total cholesterol from all patients were 191.8 (4.3) mg/dL in the SYNAREL group and 193.1 (4.6) mg/dL in the danazol group. At the end of treatment, mean values from all patients were 204.5 (4.8) mg/dL in the SYNAREL group and 207.7 (5.1) mg/dL in the danazol group. These increases from pretreatment values were significant ($p < 0.05$) in both groups.

Triglycerides were increased above the upper limit of 150 mg/dL in 12% of the patients on SYNAREL and in 7% of the patients on danazol.

At the end of treatment, no patients on SYNAREL had abnormally low HDL cholesterol fractions (< 30 mg/dL) com pared with 43% of patients on danazol. No patients on SYNAREL had abnormally high LDL cholesterol fractions (> 190 mg/dL) compared with 15% of those on danazol. There was no increase in the LDL/HDL ratio in patients on SYNAREL, but approximately a 2-fold increase in the LDL/HDL ratio in patients on danazol.

Other changes. In comparative studies, the following changes were seen in approximately 10% to 15% of patients. SYNAREL was associated with elevations of plasma phosphorous and eosinophil counts, and decreases in serum calcium and WBC counts. Danazol therapy was associated with an increase of hematocrit and WBC.

OVERDOSAGE: At present there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

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Immunohistochemical localization of prostaglandin H synthase in the female reproductive tract and endometriosis

Bradley J. Van Voorhis, MD, Phyllis C. Huettner, MD, Martin R. Clark, PhD, and Joseph A. Hill, MD

Boston, Massachusetts, and Chapel Hill, North Carolina

Prostaglandin H synthase, also known as cyclooxygenase, is an essential enzyme in prostaglandin synthesis. Using a monoclonal antibody and immunohistochemical techniques, we studied the localization of this enzyme in the female reproductive tract and in endometriosis. In the uterus, prostaglandin H synthase was primarily localized to endometrial epithelium, with surface epithelium containing more immunoreactive prostaglandin H synthase than glandular epithelium. Fallopian tube secretory epithelial cells also contained prostaglandin H synthase while ciliated epithelial cells did not. Cervical epithelium and myometrial cells did not contain prostaglandin H synthase. A higher percentage of glands in endometriosis and adenomyosis, as compared with eutopic endometrium, contained prostaglandin H synthase suggesting that these tissues are also capable of prostaglandin synthesis. These findings may have important physiologic significance in the mechanisms of embryo implantation, in menstruation, and in the pathophysiologic features of endometriosis. (AM J OBSTET GYNECOL 1990;163:57-62.)

Key words: Endometrium, endometriosis, prostaglandins, prostaglandin H synthase, cyclooxygenase

Prostaglandins have been implicated in numerous aspects of reproductive function and the human reproductive tract is an important site of prostaglandin synthesis. Tissue culture studies have demonstrated prostaglandin production by the fallopian tube,[1] myometrium,[2] and endometrium.[3] In addition, ectopic endometrium has been shown to produce prostaglandins that may contribute to the pathophysiology of endometriosis and adenomyosis.[4, 5] Although many studies have examined prostaglandin production by these tissues, few studies have attempted to localize the cells responsible for prostaglandin production. The purpose of our study was to identify the site of prostaglandin synthesis in the human fallopian tubes, uterus, and endometriosis by immunohistochemical localization of prostaglandin H (PGH) synthase, an essential enzyme in prostaglandin synthesis.

From the Fearing Research Laboratory, the Department of Obstetrics, Gynecology and Reproductive Biology, and the Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, and the Department of Obstetrics and Gynecology, University of North Carolina.

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6/1/20497

Material and methods

Patients. Tissue sections were cut from formalin-fixed paraffin-embedded specimens obtained from premenopausal women (age range 30 to 49) undergoing laparotomy for benign conditions. Uterine specimens ($n = 45$) were obtained from women at different stages of the menstrual cycle (9 menstrual phase, 11 proliferative phase, and 25 secretory phase). Tissue sections for study were obtained from the uterine fundus. Designation of menstrual cycle day was made by histologic dating. Adenomyosis was identified in nine uterine specimens, and in 18 women pelvic endometriotic tissue also was available for study. In five women tissue sections were obtained from the ampullary, isthmic, and infundibular portions of the fallopian tube and from the cervix for immunohistochemical evaluation.

Antibody. Monoclonal antibodies to PGH synthase were prepared as previously described.[6] Briefly, PGH synthase was purified from sheep seminal vesicle microsomes by chromatography on diethylaminoethyl cellulose and lentil lectin Sepharose. BALB/c mice were immunized with 50 μg of PGH synthase and screened for antibody production by immunoprecipitation and enzyme immunoassay. Splenic lymphocytes were fused to SP2/O myeloma cells. Hybridoma medium containing PGH synthase–specific antibodies, as determined by enzyme-linked immunosorbent assay and immunoblots, was used for immunohistochemistry.

Immunohistochemistry. Surgical specimens were

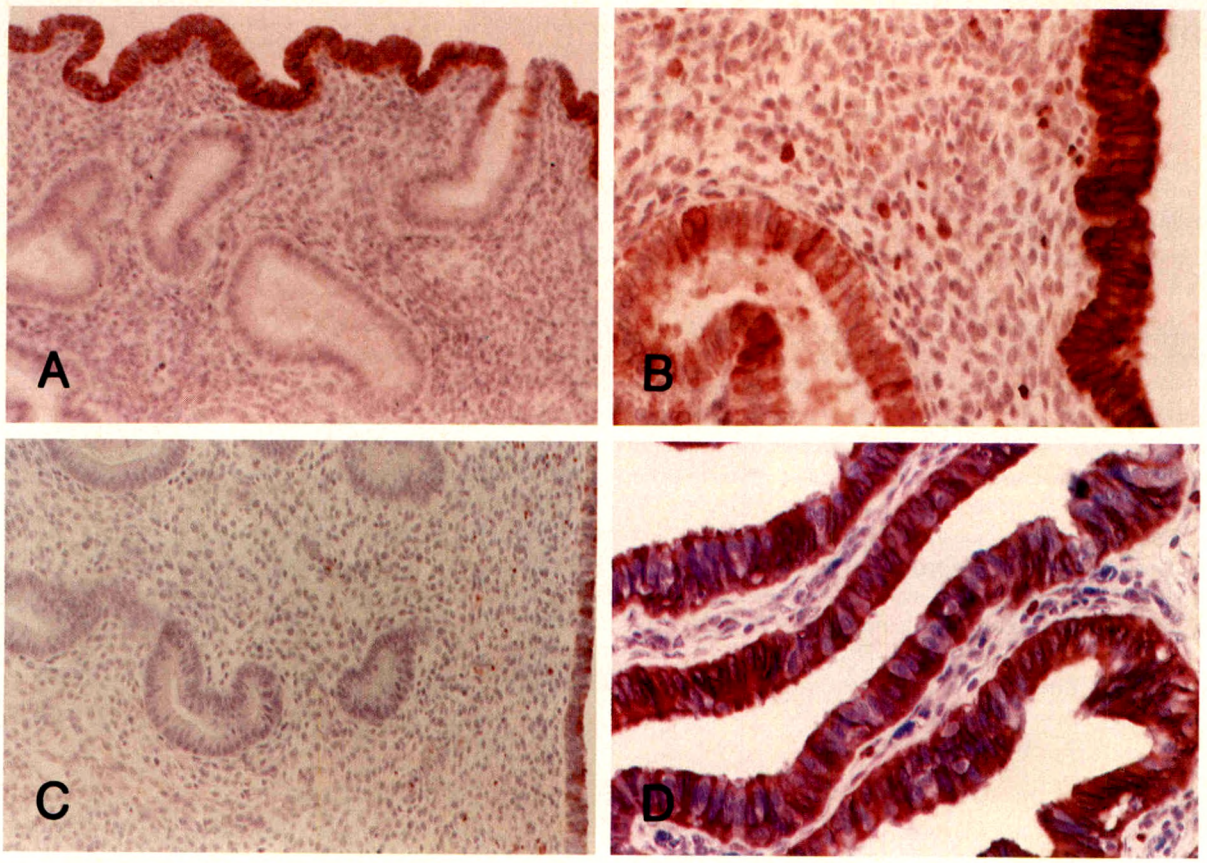


Fig. 1. A, Secretory endometrium (day 20) with positive surface epithelium. **B,** Secretory endometrium (day 19) with positive surface epithelium, glandular epithelium, and occasional stromal cells. **C,** Late proliferative endometrium with 1+ positive surface epithelium. **D,** Tubal epithelium with positive secretory cells and negative ciliated cells.

routinely fixed in neutral-buffered 10% formalin, processed, and embedded in paraffin. Sections were cut (6 μm) and mounted on slides. Dried slides were baked at 56° C for 2 hours, deparaffinized in xylene, rehydrated through an ethanol series, and treated with 3% hydrogen peroxide in methanol to block endogenous peroxidase activity. The slides were then washed in phosphate-buffered saline solution. Immunohistochemistry was performed with a streptavidin-biotin-peroxidase system (Histostain SP-kit, Zymed Laboratories, South San Francisco). Briefly, tissue sections were treated with nonimmune rabbit serum for 10 minutes to saturate nonspecific binding sites. Excess serum was blotted from the slides and then incubated with PGH synthase antibody at a 1:40 dilution in phosphate-buffered saline solution for 30 minutes at 37° C. In several specimens sequential tissue sections were stained with Dako LC (Dako Corp., Santa Barbara) substituted for anti–PGH synthase as the primary antibody. Biotinylated secondary antibody was then added (10 minutes) followed by the streptavidin-peroxidase conjugate (5 minutes) and the substrate-chromogen (aminoethylcarbazole). Finally, the tissues were counterstained with hematoxylin and mounted with an aqueous mounting solution (GVA-mount, Zymed). After each step the sections were washed with phosphate-buffered saline solution. Slides were independently interpreted by two observers. Staining was graded as 2+ for strongly reactive staining, 1+ for weakly reactive but still specific staining, and 0 for no reactivity.

The immunohistochemical specificity was determined by substitution of the primary antibody with phosphate-buffered saline solution, normal mouse serum, and nonspecific mouse immunoglobulin M (Calbiochem, La Jolla) at 2.5 μg/ml, the concentration of our PGH synthase antibody at a 1:40 dilution. In addition, the primary antibody was preabsorbed with purified PGH synthase (Oxford Biomedical Research, Oxford, Mich.) using a dilution of 10 μl of antibody and 90 μl (45 μg) of antigen before processing for immunohistochemistry.

To eliminate possible confounding effects of for-

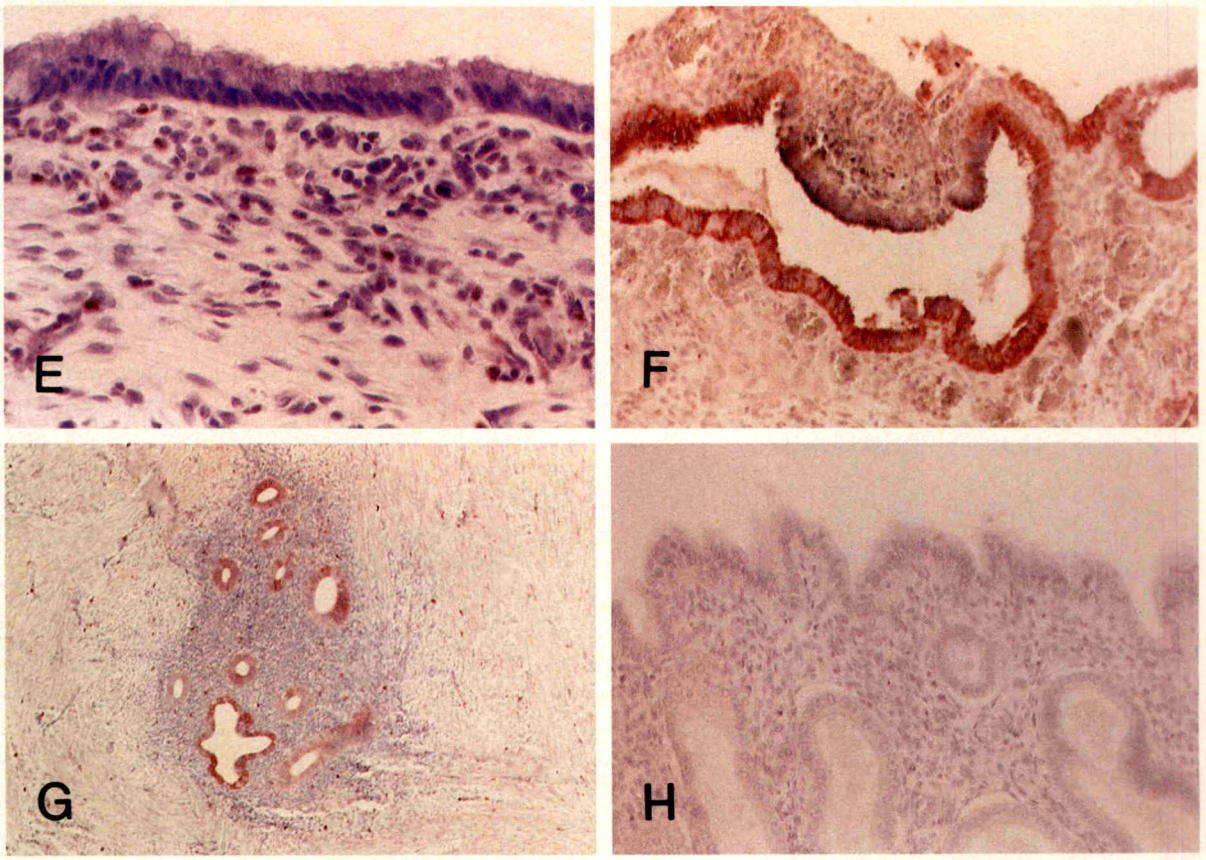


Fig. 1. E, Endocervical epithelium negative for PGH synthase. **F,** Ovarian endometriosis with PGH synthase positive epithelium. **G,** Adenomyosis with positive glandular epithelium. **H,** Secretory endometrial surface epithelium–negative control obtained after preabsorbing PGH synthase antibody with purified PGH synthase.

malin tissue fixation, five endometrial biopsy specimens from women in the secretory phase were immediately frozen in O.C.T. freezing compound (Miles Scientific, Naperville, Ill.). Slides of 6 μm cryostat sections were fixed in acetone for 10 minutes before we proceeded with immunohistochemical staining.

Western blot analysis. Endometrial specimens were removed and frozen at −70° C. Solubilization of PGH synthase was performed as previously reported[6] and Western blot analysis was performed. Polyacrylamide gel electrophoresis in sodium dodecyl sulfate was run on an 8% to 25% gradient gel in a PhastGel system (Pharmacia, Pleasant Hill, Calif.). PGH synthase standard (1.3 ng, Calbiochem, San Diego) was run in an adjacent lane. An aliquot of 4.4 μg of protein from endometrium was analyzed. Proteins were transferred to nitrocellulose with a Polyblot transfer system (American Bionetics, Hayward, Calif.). The blot was blocked with 2% nonfat dry milk dissolved in phosphate-buffered saline solution for 24 hours at 4° C, followed by an avidin-biotin blocking step. The blot was then incubated in 2.5 μg/ml anti–PGH synthase for 2 hours at room temperature and for 16 hours at 4° C. Bound primary antibody was detected with an avidin-biotin–alkaline phosphatase kit from Vector Labs (Burlingame, Calif.).

Results

In the uterus endometrial surface epithelium demonstrated the most intense immunoperoxidase staining for PGH synthase in nearly all specimens examined. In proliferative phase endometrial samples, the surface epithelium was strongly reactive in 5 of 11 specimens and weakly reactive in the remaining 6. The surface epithelium of secretory endometrium was strongly reactive in 23 of 25 specimens with the remaining specimens demonstrating weak reactivity. When surface epithelium was present in menstrual phase specimens, staining for PGH synthase was always strongly reactive. An abrupt transition in staining for PGH synthase was noted between surface epithelium and glandular epithelium at the gland openings. While surface epithelium was nearly always strongly reactive, most glandular epithelium demonstrated either weak reactivity

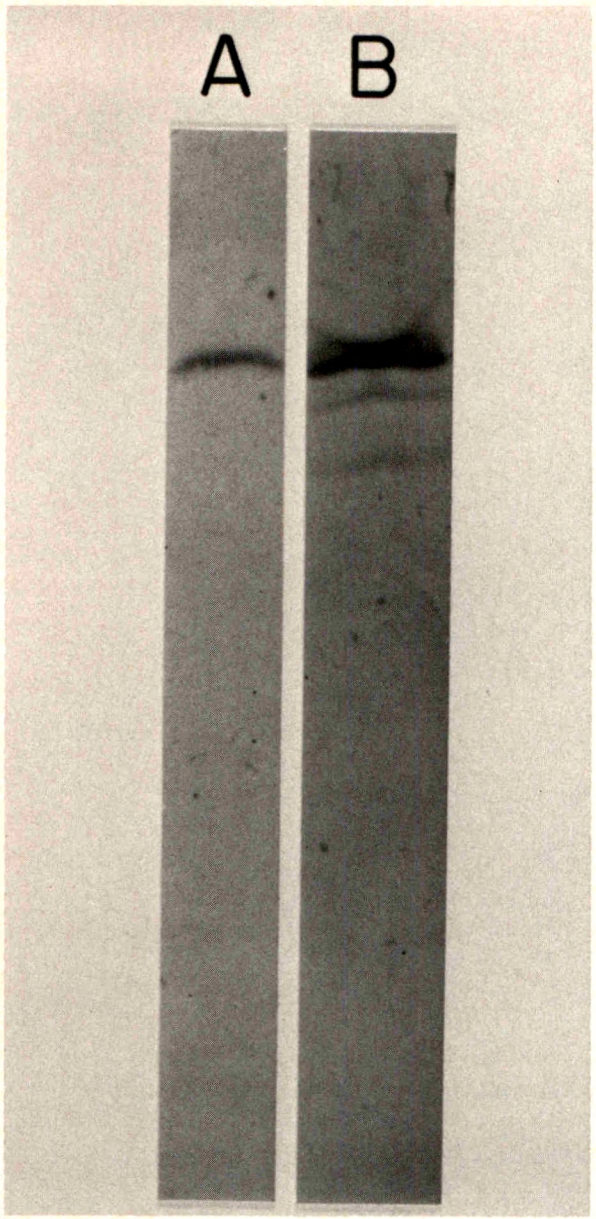


Fig. 2. Western immunoblot of 4.4 μg of protein extracted from human endometrium *(lane A)* and 1.3 μg of PGH synthase standard *(lane B)* electrophoresed on a polyacrylamide gel.

(20% of glands) or no reactivity (75% of glands). Only 5% of glands were strongly reactive. This staining pattern of glandular epithelium was consistent in menstrual, proliferative, and secretory endometrium. No distinct pattern could be discerned when glands of the stratum basalis were compared with glands of the stratum functionalis (Fig. 1, *A*, *B*, and *C*).

Scattered endometrial stromal cells were strongly reactive with an average density of three positive cells per high-power field. However, a large majority of stromal cells were negative. No differences in positively stained cell density was observed when sections from different phases of the cycle were compared (Fig. 1, *B*).

Myometrial cells did not stain for PGH synthase, but scattered positive cells were seen in the interstitial connective tissue at an average density of 15 positive cells per high-power field (×400). These cells were present in all uterine specimens, and no differences were noted at different phases of the menstrual cycle. The positive cells were of white blood cell origin on the basis of morphologic features and positive staining with the white blood cell antibody Dako LC.

In the fallopian tube, mucosal secretory cells were intensely (2+) reactive for PGH synthase. Ciliated mucosal cells and cells in the connective tissue of the lamina propria were negative. The smooth muscle of the fallopian tube was weakly (1+) reactive. No difference in this pattern was seen when tissue from different areas of the fallopian tube were compared (Fig. 1, *D*).

In the cervix the columnar epithelium lining the endocervical canal and the epithelium of cervical glands were negative for PGH synthase. The squamous epithelium of the cervix also was negative. Rare scattered positive cells were present in the connective tissue of the cervix. Vascular smooth muscle present in uterine specimens was only weakly reactive for PGH synthase while vascular endothelium was negative (Fig. 1, *E*).

A higher percentage of ectopic endometrial glands demonstrated intense reactivity as compared with normal endometrial glands. In 9 specimens of adenomyosis, a median of 40% of glands were intensely stained (range 5% to 75%). In 18 specimens of endometriosis, a median of 50% of glands were intensely stained (range 0% to 100%). In 9 cases of ovarian endometriomas, the epithelial cyst lining was always strongly positive. Rare stromal cells around the ectopic endometrial glands also were strongly positive. No distinct patterns could be discerned when pathologic specimens from different phases of the menstrual cycle were compared (Fig. 1, *F* and *G*).

When multiple sections of the same tissue specimen were examined, identical staining patterns were observed in each section. No staining was observed in control sections when the PGH synthase antibody was replaced with phosphate-buffered saline solution, normal mouse serum, or nonspecific mouse IgM. Preabsorbing the antibody with purified PGH synthase also resulted in no staining of tissue (Fig. 1, *H*). Fresh-frozen endometrial tissue sections demonstrated identical staining patterns as seen in formalin-fixed tissues.

On gel electrophoresis and Western blotting, the PGH synthase antibody reacted with purified sheep PGH synthase. Analysis of protein extracted from human endometrium revealed cross-reactivity with an antigen that comigrated with the sheep PGH synthase.

The approximate relative molecular mass of the proteins was 72 kd (Fig. 2).

Comment

Prostaglandins are involved in many physiologic processes in the female reproductive tract. Investigators have proposed a role for prostaglandins in tubal motility[1] and menstruation.[7] In addition, animal studies have implicated prostaglandins in uterine implantation of the embryo and the decidual cell reaction.[8, 9] Many investigators have studied the in vivo and in vitro production of prostaglandins by human reproductive tract tissues, but cellular localization of prostaglandin synthesis within these tissues has not been systematically performed.

PGH synthase, also known as cyclooxygenase, is an essential enzyme in prostaglandin synthesis as it is the first enzyme of the pathway in which arachidonic acid is converted to prostanoids such as prostacyclin, thromboxane A_2, and prostaglandins E_2 and $F_{2\alpha}$. The purpose of this study was to identify the cells containing PGH synthase in the human female reproductive tract and in endometriotic tissue by immunohistochemical techniques. The monoclonal antibody we used, although produced against sheep PGH synthase, is not species-specific but rather cross reacts with PGH synthase from many other species,[6] including humans.[10] This was confirmed by our Western blot analysis, which demonstrated antibody reactivity with a human antigen that comigrated with sheep PGH synthase standard on gel electrophoresis. The approximate relative molecular mass of 72 kd correlates well with previously published studies characterizing the enzyme.[11]

In uterine specimens, the most intense staining for PGH synthase occurred in the surface epithelium of the endometrium. An obvious difference in staining between the surface and glandular epithelium could be discerned starting abruptly at the gland neck. In contrast to the uniformly intense staining of surface epithelium, only 5% of glands were intensely stained and most (75%) were negative for PGH synthase. The possibility that surface epithelium and glandular epithelium have differing cellular characteristics has been previously suggested. Lee and Damjanov,[12] utilizing soybean agglutinin for histochemical identification of terminal *N*-acetylgalactosamine, demonstrated staining of surface but not glandular epithelium. Using electron microscopy, Ferenczy et al [13] detected morphologic differences between these cell types. The presence of immunoreactive PGH synthase in surface epithelium suggests it is capable of prostaglandin synthesis. In animal studies there is increasing evidence that the luminal epithelium may synthesize prostaglandins at the time of implantation. In the mouse, Kennedy[8] has suggested that luminal epithelial cells may respond to embryonic signals by initiating prostaglandin synthesis. The prostaglandins may then diffuse into the underlying stroma to increase vascular permeability. Parr et al.[9] studied immunohistochemical localization of prostaglandin synthase in the rat uterus at implantation and noted staining of both luminal epithelium and adjacent decidualized stromal cells. Further work is needed to determine if surface epithelium prostaglandin synthesis is important in human implantation.

In addition to PGH synthase–positive cells in the endometrial epithelium, occasional positive cells were noted in the uterine stroma and interstitial connective tissue of the myometrium. Myometrial cells and the majority of stromal cells were negative for PGH synthase. The positive cells noted in myometrial connective tissue are leukocytic cells on the basis of morphologic features and positive staining with a monoclonal antibody to leukocytes, Dako LC. Uterine stroma is made up of a heterogeneous population of cells including uterine stromal cells and leukocytes.[14] The precise cell type in the stroma that contained PGH synthase could not be positively identified because of obscuring of morphologic features by peroxidase staining. We propose that these cells may be macrophages, which are known to produce prostaglandins.[15]

Prostaglandin production by the human endometrium increases during the luteal phase.[7] To determine if an increase in immunoreactive PGH synthase could contribute to increased prostaglandin synthesis in the human luteal phase, endometrium from different days of the cycle was examined. We found increased immunostaining of surface epithelium in the luteal phase as compared with the proliferative phase. However, no differences in staining of glands, stromal cells, or myometrium could be demonstrated.

One previous immunohistochemical study of PGH synthase in the human uterus has been performed. Rees et al.[16] noted intensely positive staining of all surface epithelium and most glands in luteal phase specimens. In contrast to our study, they noted no specific staining in any proliferative phase specimens or in the uterine stroma or myometrium. Tissue explant studies support our findings as they have demonstrated prostaglandin production by proliferative phase endometrium and separated stromal cells, suggesting that PGH synthase is present in these tissues.[5] Difference between these two studies might be accounted for by use of different antibodies and by their use of unfixed tissue.

We observed immunoreactive PGH synthase in the tubal mucosal secretory cells, while ciliated cells of the tubal mucosa were negative. Interestingly, the smooth muscle of the fallopian tube contained immunoreactive PGH synthase, in contrast to the myometrium, which was negative. Our findings of immunoreactive PGH synthase support previous studies that have demon-

strated prostaglandin production by the human fallopian tube.[14]

In the cervix no staining of endocervical lining, glandular epithelium, or squamous epithelium was observed. Obvious differences in immunoreactive prostaglandin synthase content were noted when epithelium of the cervix was compared with uterine surface epithelium. These results indicate that epithelium derived from the müllerian duct differs in PGH synthase content depending on location and differentiation.

Prostaglandin production by endometriotic tissue has been demonstrated in vitro. Vernon et al.[4] demonstrated differing capacities of prostaglandin production by endometriotic implants on the basis of gross morphologic features of the lesion. They speculated that lesions producing large amounts of prostaglandin were "early" implants with increased numbers of functional glands present. Our findings also would suggest that glandular epithelium in endometriosis may be important in prostaglandin synthesis as prostaglandin synthase was primarily localized in this epithelium. Forty percent of endometriotic glands and the epithelium of all ovarian endometriomas were intensely positive for PGH synthase. Glandular epithelium in adenomyosis also stained intensely for PGH synthase. Ectopically located glands in both adenomyosis and endometriosis were more often intensely positive for PGH synthase than eutopic endometrial glands (50% vs 5%). This further supports the concept that ectopic and eutopic endometrium are dissimilar.

Our findings indicate that the epithelium of the female reproductive tract contains immunoreactive PGH synthase. Within the epithelial layer, levels of PGH synthase vary depending on location and cellular differentiation. Surface epithelium of the endometrium stains intensely for PGH synthase and has more immunoreactive PGH synthase than glandular epithelium. Ectopic glandular epithelium in endometriosis and adenomyosis also contains PGH synthase. Although staining of PGH synthase cannot be equated with levels of prostaglandins produced, our findings suggest that endometrial surface epithelium and glandular epithelium in endometriosis and adenomyosis are capable of prostaglandin synthesis.

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A case of Rh isoimmunization: Should threatened first-trimester abortion be an indication for Rh immune globulin prophylaxis?

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Despite the recommended 28 weeks' gestation antenatal, postnatal, and postabortion prophylaxis with Rh immune globulin, residual Rh immunization still occurs in Rh-negative women. We describe a patient whose history suggests development of an anti-D antibody after first-trimester bleeding. To our knowledge, this is the first such case reported in the English literature. (AM J OBSTET GYNECOL 1990;163:63-4.)

Key words: Rh isoimmunization; bleeding, first trimester; Rh immune globulin, indications

Antepartum bleeding without loss of the conceptus carries some risk of transplacental hemorrhage. However, threatened abortion in the first trimester of pregnancy is not typically included in published lists of indications for Rh immune globulin administration.

We report a case of a 35-year-old $Rh_o(D)$-negative woman who was seen between 8 and 9 weeks' gestation with vaginal bleeding and a viable intrauterine pregnancy verified by ultrasonography. Because the pregnancy was not terminated, Rh immune globulin was not administered. The patient received Rh immune globulin at 15 weeks' (after amniocentesis) and 29 weeks' gestation.

Since vaginal bleeding in the first trimester of pregnancy occurs commonly, Rh immune globulin administration to all $Rh_o(D)$-negative women with threatened abortion could be costly. However, many believe the benefits of avoiding any possible cases of Rh isoimmunization outweigh the costs.[1] The present case offers support for administration of Rh immune globulin to $Rh_o(D)$-negative women with significant vaginal bleeding in the first trimester of pregnancy.

Case report

A 35-year-old woman, gravida 6, para 1-0-4-1, was seen in an emergency department in the eastern United States on Sept. 6, 1988, complaining of pelvic cramping and passage of blood clots through the vagina. Her last normal menstrual period was on June 9, 1988.

Her past obstetric history was significant for four elective abortions and one live birth of an $Rh_o(D)$-negative child. The previous birth was of a child fathered by her first husband whose blood type was O, $Rh_o(D)$ negative. The current pregnancy was with a second husband. Administration of Rh immune globulin was documented for the first and most recent abortions. According to the patient, it was also given after the other two abortions. The antibody screen was negative at the time of first abortion and first delivery. Other records are no longer available. The patient denied any history of blood product transfusion other than Rh immune globulin.

At the time of the emergency department visit in 1988, a speculum examination revealed a cyanotic gravid cervix with a closed os. A small amount of red-brown discharge was observed in the vaginal vault.

An abdominal ultrasonogram revealed a viable fetus estimated to be 8.5 weeks' gestational age. Neither maternal blood typing nor the Kleihauer-Betke test was performed.

The patient was discharged from the emergency department and advised to follow up with her local obstetrician. Rh immune globulin was not given.

On Sept. 20, 1988, the patient was seen for the first time in a local obstetric clinic, and routine prenatal laboratory studies were performed. The patient's blood type was A, $Rh_o(D)$ negative, and an antibody screen was negative with low-ionic-strength saline solution and two-stage papain enzyme technique.

On Oct. 20, 1988, amniocentesis with ultrasonographic guidance was performed at another facility for genetic counseling. Ultrasonography revealed a 15-week, anatomically normal fetus. An antibody screen

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performed with low-ionic-strength saline solution only was negative, and therefore 300 μg of Rh immune globulin was given intramuscularly.

On Feb. 1, 1989 (approximately 29 weeks' gestation), the patient transferred her care to our institution. A routine antibody screen was positive, with anti-D specificity in low-ionic-strength saline solution with indirect antiglobulin testing and with two-stage papain techniques. Initial communications between our transfusion service and prior care givers suggested that these findings could be consistent with passive antibody, and 300 μg of Rh immune globulin was given intramuscularly for routine antenatal prophylaxis.

On April 6, 1989 (approximately 39 weeks' gestation), the patient was delivered of a live, 3330 gm female infant. The infant's cord blood type was O, $Rh_o(D)$ positive, and the direct antiglobulin test was strongly positive on cord blood cells. Rh immune globulin was released on the basis of the belief that the infant's positive direct antiglobulin test was secondary to antenatal maternal Rh immune globulin. At a subsequent transfusion service case review, the discrepancy of the strong positive cord blood direct antiglobulin test was noted and maternal anti-D quantitation was performed on an immediate postpartum serum specimen. The maternal IgG anti-D titer was 1/4096. A repeat screen at 6 months post partum continued to show anti-D with a titer of 1/1024. The infant's bilirubin level was 2.6 μ/dl at birth and rose to a peak level of 9.3 μg/dl on the seventh day. The infant's hemoglobin was 10.5 gm/dl on the seventh day and dropped to a nadir of 8.5 gm/dl on the fourteenth day.

Comment

According to *Williams' Obstetrics*, eighteenth edition (Appleton & Lange), one of every four or five women has vaginal spotting or heavier bleeding during the early months of pregnancy. Of those, only half subsequently have complete abortion. There does not seem to be a clear consensus in the literature on the use of Rh immune globulin for first-trimester bleeding without loss of the conceptus in $Rh_o(D)$-negative women. Some authors include this situation in their recommendations for Rh immune globulin use.[1] Some do not discuss threatened abortion in reviews of Rh immune globulin prophylaxis,[2] while others recommend making a decision on the basis of determinations of fetal cells in the maternal circulation.[3] It has been established that a very small volume of $Rh_o(D)$-positive blood can sensitize an $Rh_o(D)$-negative individual[1] and, for this reason, use of Rh immune globulin has been advised for routine prophylaxis after chorionic villus sampling as early as 8.5 weeks.[3]

Our case illustrates three important points. First, it is possible to become $Rh_o(D)$ sensitized after a minor first-trimester hemorrhage with resultant risk of hemolysis in the infant. Had this case represented an amnestic response from a previous exposure, anti-D should have been apparent with enzyme testing at the time of the first screening test in light of the bleeding episode 2 weeks previously. The patient received adequate prophylaxis with Rh immune globulin for the amniocentesis, and no other obvious events would explain the sensitization that occurred during the pregnancy. Second, although antenatal maternal Rh immune globulin is probably the most common explanation for a neonatal positive direct antiglobulin test with anti-D specificity, a strongly positive newborn direct antiglobulin test should be carefully reviewed to avoid missing a case of maternal sensitization. Third, although obstetricians and gynecologists may be aware that Rh immune globulin should be given when there is doubt, emergency department personnel may not. On the basis of the example of this case, our institution will be revising its recommendations for the use of Rh immune globulin to include first-trimester bleeding in $Rh_o(D)$-negative women, regardless of whether they do undergo abortion. Our revised guidelines will be given to our Emergency Medicine staff as well as to physicians in obstetrics and gynecology.

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Antisperm antibodies in women undergoing intrauterine insemination

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Intrauterine insemination is widely used for the treatment of infertility as a result of cervical or male factors or empirically before in vitro fertilization or gamete intrafallopian transfer. This study was designed to confirm or refute the theoretical concern that intrauterine insemination may induce antisperm antibodies in such women. Serum and cervical mucus were obtained at the first, fourth, and sixth intrauterine inseminations. The serum was screened by the Immunobead test for IgG and IgA. If screening results were positive (>10% binding), antisperm antibodies were titered by the microimmobilization and microagglutination tests. The Immunobead test was performed on the cervical mucus after liquefication with bromelin. Ninety-three patients were followed up prospectively. Of these, 40 completed six intrauterine insemination cycles and the remaining 53 completed four cycles. Low transient antisperm antibody levels were detected in 10.8% of the patients and would not be expected to affect the prognosis for fertility. It is concluded that intrauterine insemination does not induce significant antisperm antibody production in women. (AM J OBSTET GYNECOL 1990;163:65-8.)

Key words: Antisperm antibodies, intrauterine insemination, cervical mucus, immune factor infertility

Intrauterine insemination is an accepted therapeutic modality for the treatment of infertility caused by abnormalities in the cervical mucus, semen analysis, or sperm-mucus interactions. It is also used as empiric treatment for infertility as a result of other causes, including unexplained infertility, before more expensive and invasive in vitro fertilization and gamete intrafallopian transfer procedures are considered.[1] Several studies have suggested that intrauterine insemination during superovulation cycles further improves pregnancy rates.[2-4] There is a hypothetical concern that intrauterine insemination may sensitize the patient to produce antisperm antibodies.[1, 5] This may be attributed to the greater number of sperm (antigenic load) entering the upper genital tract and peritoneal cavity and the inoculation schedule. In addition, the sperm-washing procedure removes seminal immune suppressor factors.[6-9] Previous studies concluded that sensitization does not occur to a significant degree with intrauterine insemination; however, the numbers of study patients were small, the number of cycles was not standardized, and no attempt was made to identify antisperm antibodies in the cervical mucus.[10, 11] The goal of this study was to provide a more definitive answer by addressing these factors.

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Material and methods

Ninety-three patients undergoing intrauterine insemination therapy for infertility were studied prospectively. The indication for intrauterine insemination was dysmucorrhea (n = 19), male factor (n = 25), poor mucus plus male factor (n = 3), poor result of Huhner test (with good mucus and normal semen analysis, n = 23), and empiric treatment (n = 23). Serum and cervical mucus were obtained at the time of the first, fourth, and sixth intrauterine inseminations (i.e., baseline and after the completion of three and five cycles, respectively). Not unexpectedly, several mucus specimens were insufficient for analysis, especially in the group with dysmucorrhea. Patients who conceived before the fourth cycle were excluded. No patient received more than six intrauterine insemination treatments. All patients received either clomiphene citrate or human menopausal gonadotropins. Human chorionic gonadotropin, 5000 U intramuscularly, was administered when transvaginal ultrasonography revealed one or more follicles with a mean diameter at least 18 mm in the group treated with clomiphene citrate or 16 mm in the group receiving human menopausal gonadotropins. Intrauterine insemination was timed 28 to 36 hours later.

Sperm preparation and insemination. All semen

Table I. Positive antisperm antibody results

Patient No.	*Cause*	*Cycle No.*	*Serum Immunobead (location)*	*Microagglutination test*	*Cervical mucus (Immunobead)*
1	Poor mucus	1	IgG(A), IgA (PA, MP, TT)	1:8	—
		4	—	—	—
		6	—	—	—
2	Empiric	1	—	—	—
		4	IgG (A, PA, MP, T, TT)	—	—
3	Poor mucus	1	—	—	—
		4	IgG (TT)	—	—
		6	—	—	—
4	Empric	1	IgG (A, T)	—	—
		4	IgG (A, T)	—	—
5	Male factor	1	IgG (A, TT)	—	IgA (A)
		4	IgG (A, PA, MP, T, TT)	—	IgA (A, TT)
6	Poor mucus	1	—	—	—
		4	IgG (A, MP)*	—	—
7	Poor mucus	1	—	—	—
		4	IgG (A, MP, T, TT)	—	—
8	Male factor	1	IgA (A, TT)	—	—
		4	—	—	—
		6	—	—	—
9	Empiric	1	—	—	—
		4	IgA (A)	—	—
10	Poor result of Huhner test	1	IgG (A)	1:16	—
		4	—	—	—
		6	—	—	—

A, Acrosome; *PA*, postacrosome; *MP*, midpiece; *T*, tail, *TT*, tail tip.
*Remained positive for 4 months, negative at 6 months.

specimens were obtained from the husband by masturbation into a sterile jar. No donor inseminations were included. After liquefaction a small aliquot was removed for semen analysis with a Makler chamber. The specimen was washed twice by centrifugation at 800 *g* for 5 minutes in Ham's F-10 media (Gibco, Grand Island, N.Y.). The final pellet was resuspended in 0.3 ml of media, without swim-up, and the sperm concentration and motility were recorded. The total volume inseminated was 0.4 to 0.5 ml. The exocervix was wiped with a cotton ball and the cervical mucus was aspirated into a tuberculin syringe. Intrauterine insemination was accomplished with a Unimar intrauterine catheter (Unimar, Wilton, Conn.) and blood was obtained by venipuncture. The serum and cervical mucus specimens were frozen for later antisperm antibody assay at the completion of the study. Only one insemination was performed each cycle. Three donors with proved fertility and negative direct Immunobead testing provided the sperm for the assays. Direct Immunobead testing was performed selectively on the patients' husbands when agglutination was noted on semen analysis, the Huhner test result was abnormal with good cervical mucus (i.e., immotile or shaking sperm), or with long-standing unexplained infertility.

Cervical mucus liquefaction.[12-14] The cervical mucus was liquefied by addition of an equal volume of Tyrode's solution (Sigma, St. Louis, Mo.) with 0.3% bovine serum albumin (Sigma) containing 2 mg/ml of bromelin (Sigma). The mixture was aspirated repeatedly through a 22-gauge needle until it was completely liquefied (up to 60 minutes at room temperature). For a few specimens, additional bromelin was required to achieve full liquefaction. The mixture was then centrifuged at 800 *g* for 10 minutes. The supernatant was removed and heat-inactivated at 56° C for 30 minutes.

Indirect Immunobead test.[15, 16] The liquefied donor semen specimen was adjusted with Tyrode's solution to a concentration of 6 to 9 × 10^6 motile sperm per milliliter and 100 μl incubated with 200 μl heat-inactivated patient's sera for 1 hour at 37° C. The sperm were washed three times in 5 ml of Tyrode's solution with 0.3% bovine serum albumin at 800 *g* for 5 minutes at 37° C. The final sperm pellet was resuspended in 100 μl Tyrode's solution with 5% bovine serum albumin. The Immunobeads were prepared by washing 200 μl of 5 mg/ml of rabbit antihuman IgG–and IgA–bound latex beads (Bio-Rad, Richmond, Calif.), each in 10 ml of Tyrode's solution with 0.3% bovine serum albumin, as was done for the sperm. The bead pellets were resuspended in 200 μl of Tyrode's solution with 5% bovine serum albumin. Finally, 5 μl of each Immunobead solution was incubated separately with 5 μl of serum-reacted sperm on a glass slide for 5 minutes, then examined by phase-contrast microscopy (×400). At least 10% of the motile sperm must be bound by

beads for the result to be considered positive. The locations of bead attachment were also recorded. All specimens were run with known positive and negative control sera. The Immunobead test on the liquefied cervical mucus was identical. The entire volume of cervical mucus supernatant, up to 200 μl, was used for the assay.

Because no positive cervical mucus control was available, a positive serum control treated in an identical fashion as the mucus served as the positive control. In addition, an untreated aliquot of the same positive control serum was run as a further control. Bromelin treatment of the positive control serum did not affect the results of Immunobead testing with any of the assays used in this study.

Modified microagglutination test.[17] Heat-inactivated patients' and positive control sera were serially diluted with Tyrode's solution from 1:4 to 1:128, and 5 μl of each dilution was added to the wells of a Terasaki tissue culture tray containing 5 μl of paraffin oil per well. Donor semen was adjusted with Tyrode's solution to a sperm concentration of 25 to 30 × 10^6 ml, 1 μl of which was added to each well. The tray was incubated at room temperature for 2 to 3 hours and was then examined with an inverted phase-contrast microscope. The highest titer exhibiting sperm agglutination was reported. Tyrode's solution plus sperm served as a negative control.

Modified microimmobilization test.[18] Patients' and positive control sera were serially diluted and added to a Terasaki tray with paraffin oil as in the modified microagglutination test. To each well 1 μl guinea pig complement (Gibco) was added. Tyrode's solution plus complement, and patients' sera with heat-inactivated complement, were the negative controls. Donor semen was adjusted to 40 to 60 × 10^6 sperm per milliliter and 1 μl added to each well. The tray was incubated for 1 hour at 37° C, then examined on an inverted phase-contrst microscope. The highest dilution with >50% immobilization was reported.

Results

Forty patients completed six intrauterine insemination cycles and an additional 53 completed four cycles. The 10 patients (10.8%) who tested positive for antisperm antibodies are summarized in Table I. No patient had a positive serum microimmobilization test or cervical mucus positive for IgG on Immunobead testing. Of the 10 patients with positive serum Immunobead testing, seven had IgG, two had IgA, and one had both. One patient had IgA on the cervical mucus Immunobead test. The serum was also positive for IgG.

The mean and standard deviation of the concentration of total sperm inseminated (millions per milliliter) was 126.5 ± 80.2 for the unsensitized group and 124.5 ± 57.3 for the sensitized group. The concentration of motile sperm inseminated was 61.2 ± 50.3 and 76.9 ± 75.4 for the two groups, respectively. Statistical analysis with analysis of variance revealed no significant difference between sensitized and unsensitized women for postwash total concentration ($p = 0.96$) and for postwash motile concentration ($p = 0.38$). Fifty-five (59.1%) of the husbands were tested for antisperm antibodies. Nine of 51 (17.6%) of the husbands of unsensitized women tested positive, compared with one of four (25%) of the husbands of sensitized patients. The percentage of husbands with positive antisperm antibodies was not significantly different between the two groups of women (Fisher's exact test, $p = 0.56$).

Comment

Kremer[19] reported that intrauterine insemination led to an increase in antisperm antibody titers in five of five women previously sensitized; however, none of the 20 unsensitized women developed antisperm antibodies after six intrauterine insemination cycles. Overstreet et al.[20] retested the initial sera on 13 of 14 patients that had become sensitized (30% to 50% binding on Immunobead testing) after two to 13 cycles. Five of these were positive (20% to 40% binding) on retesting. They concluded that low levels of antisperm antibodies may be significantly increased as a result of intrauterine insemination. Moretti et al.[10] tested sera of 41 patients before and after one to 15 intrauterine insemination cycles with agglutination and immobilization assays and the Immunobead testing. One patient had a low agglutination titer initially, which remained unchanged after nine intrauterine insemination cycles. Another patient had a positive agglutination and Immunobead test for IgG and IgM after a single insemination. A third patient converted to a positive immobilization test after nine cycles. Horvath et al.[11] performed the Immunobead test on sera at baseline and serially up to six intrauterine insemination cycles. All patients were treated with human menopausal gonadotropins or clomiphene citrate and human menopausal gonadotropins. Twenty-eight patients received intrauterine insemination and 25 served as controls. Only 10 patients in the intrauterine insemination group completed six cycles. They demonstrated no significant difference in antisperm antibody levels between the two groups.

Our data indicate that there is no significant induction of antisperm antibody production in unsensitized women, or increase in low antisperm antibody titers present at baseline. Because no patients in our series had high antisperm antibody titers initially, we cannot address what effect intrauterine insemination would have in this situation. Higher total and motile sperm concentrations or the presence of antisperm antibodies

on the husbands' sperm did not predispose the development of antisperm antibodies.

The Immunobead test was selected as the screening test because it provides additional information with regard to the antibody class and the regions of the sperm bound by antibody. It is also less subject to nonspecific binding than the agglutination and immobilization assays. We used an arbitrary positive threshold of 10% Immunobead binding to define a positive antibody reaction in hopes of improving sensitivity. It should be noted that all of our patients with a positive Immunobead test result had Immunobead binding below 50%. Horvath et al.[11] noted that there are no data that correlate the percentage of Immunobead binding with subsequent conception rates. Although the clinical implication of our low threshold is unknown, it should be recognized that it was often associated with a serum microagglutination test titer of <1:8, which is rarely correlated with infertility.

In our study only one patient (1.1%) had a positive Immunobead test result on the cervical mucus. This result is lower than that reported previously.[14,15] Earlier studies demonstrated a strong correlation between cervical mucus Immunobead test positivity and positive serum immobilization testing. In our series no patient had a positive serum immobilization test. These discrepancies may be attributed to differences in patient populations. In addition, since antisperm antibodies may enter the cervical mucus by transudation from the vascular system, the low serum levels may have been inadequate to yield a sufficient concentration in the cervical mucus to exceed the sensitivity of the Immunobead test. That our patient had IgA in the cervical mucus and IgG in serum suggests that the IgA was produced locally in the cervix. Degradation of immunoglobulins by the proteolytic enzyme bromelin, which was used to liquefy the cervical mucus, has been discounted by previous investigators.[12-15] To further ensure that the low incidence of cervical mucus antisperm antibodies was not a result of an effect of bromelin, we treated positive control sera in an identical fashion to the cervical mucus and found no alteration in antisperm antibody test results. Currently there is no clinical method to assess the uterine and fallopian tube environments for local antisperm antibody production.[11]

In summary, our data provide further support to reduce the concern that intrauterine insemination may commonly induce significant antisperm antibody production in unsensitized women or increase titers in those with preexisting low levels. Whether intrauterine insemination will further raise high antisperm antibody titers remains open to speculation. More importantly, the broader questions regarding the value of intrauterine insemination and the clinical significance of antisperm antibody are still unresolved.

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Expression of P-glycoprotein in epithelial ovarian cancer: Evaluation as a marker of multidrug resistance

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The multidrug-resistance gene, MDR1, encodes a plasma membrane glycoprotein termed P-glycoprotein that mediates active cellular efflux of certain chemotherapeutic agents. P-Glycoprotein expression was evaluated in 98 frozen tumor specimens from 57 patients with epithelial ovarian cancer by the indirect immunoperoxidase technique with monoclonal antibodies C219 and JSB-1 used for detection. Tumor specimens were further characterized antigenically with a panel of monoclonal antibodies representing a variety of epithelial cell antigens. Included were 57 specimens from 33 previously untreated patients; 11 specimens were also available from eight patients in this group after chemotherapy. An additional 30 specimens were studied from 24 other patients after chemotherapy. In only four of the 57 patients with ovarian cancer (7%) did one or more of the specimens express P-glycoprotein. Two of these patients had tumors that were considered clinically drug resistant. No increase in P-glycoprotein expression was noted after exposure to chemotherapy, including the eight individuals for whom specimens were available both before and after treatment. Although drug resistance is a major problem in treatment of ovarian cancer, resistance to the drugs most active against these tumors probably occurs through a mechanism other than expression of the MDR1 gene product. (Am J Obstet Gynecol 1990;163:69-73.)

Key words: P-Glycoprotein, multidrug resistance, ovarian cancer, chemotherapy

Resistance to cytotoxic drugs by ovarian cancer cells is a major problem in the treatment of this disease. Approximately 75% of ovarian cancers respond initially to combination chemotherapy. The remaining 25% can be considered primarily resistant to chemotherapy. However, among the initial responders, all but approximately 15% to 20% of patients eventually have a relapse, with tumors subsequently displaying resistance to multiple chemotherapeutic agents. Thus some 80% of ovarian cancers are ultimately resistant to chemotherapy. Although the mechanisms of action of the various cytotoxic drugs are now fairly well understood, the mechanisms by which cancer cells are able to resist these effects are only beginning to be elucidated.

By means of tissue culture techniques, it has been observed that the exposure of tumor cells to relatively low concentrations of a particular cytotoxic agent may induce resistance not only to that agent but also to multiple other agents to which the tumor cells have never been exposed. This phenomenon has been termed multidrug resistance. One mechanism by which multidrug resistance may occur takes place at the level of the cell's plasma membrane. A high-molecular-weight glycoprotein, termed P-glycoprotein, has been found specifically associated with the plasma membrane in cells that display multidrug resistance, including some animal and human ovarian cancer cells,[1] where it may act as an energy-dependent efflux pump that removes toxic compounds from the cell. P-Glycoprotein is encoded by a gene, designated MDR1, that has homologies to other genes that encode membrane transport proteins. Monoclonal antibodies have been developed that detect P-glycoprotein in tissues, and preliminary reports have appeared examining its expression in human ovarian cancer.[2]

This study examines the expression of the MDR1 gene product in human ovarian cancers by means of monoclonal antibodies that detect P-glycoprotein, in an attempt to define the role this mechanism of drug resistance may play in ovarian cancer. Tumor specimens were further characterized with a panel of monoclonal antibodies representing a variety of epithelial cell antigens with known patterns of reactivity in ovarian cancer.[3]

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Table I. P-glycoprotein expression of ovarian cancers by histologic cell type

Ovarian cancer cell type	Total		No. of patients with positive* specimens	
	No. of patients*	No. of specimens	MAB C219	MAB JSB-1
Serous	35	61	3	3
Serous borderline	3	3	0	0
Endometrioid	6	13	0	0
Clear cell	2	3	0	0
Mucinous	2	6	0	0
Undifferentiated	9	12	1	1
TOTAL	57	98	4	4

MAB, Monoclonal antibody.

*Many patients had multiple specimens tested from either the same operation or a subsequent procedure. Expression of P-glycoprotein did not vary among a given patient's specimens. Thus results are expressed by patient rather than by specimen.

Material and methods

Monoclonal antibodies. Murine monoclonal antibodies C219 (IgG2a) (Centocor, Malvern, Pa.) and JSB-1 (IgG1) (Bio/Can America, Portland, Maine), which recognize different internal epitopes of the P-glycoprotein molecule,[4, 5] were used as purified immunoglobulin at a concentration of 20 μg/ml or as diluted ascites (1:200), respectively. All tumor specimens were also characterized antigenically with a panel of monoclonal antibodies that included MH99 (IgG2a), MW162 (IgM), MX35 (IgG1), MW207 (IgG1), MT334 (IgG1), and A33 (IgG2a), all generated and characterized in our laboratory,[3] as well as OC125 (IgG1) (provided by Dr. R. Bast, Duke University).

Immunohistologic analysis. Tumor specimens were obtained at the time of laparotomy in 57 patients with epithelial ovarian cancer. Complete clinical information was available for all patients. Specimens were frozen in isopentane cooled in liquid nitrogen, embedeed in O.C.T. compound (Labtech, Naperville, N.C.), and stored at −70° C until cryosectioning. Tissue sections were cut at 6 μm, fixed for 10 minutes with cold acetone, and treated with 1% hydrogen peroxide to remove endogenous peroxidase activity. Detailed methods of the indirect immunoperoxidase technique have been described previously.[3] Briefly, tissue sections were incubated with monoclonal antibody for 90 minutes at room temperature, washed with phosphate-buffered saline solution, incubated with peroxidase-conjugated rabbit anti-mouse IgG (Dako, Santa Barbara, Calif.) for 60 minutes, and then washed again. The antigen-antibody complexes were visualized with diaminobenzidine (Sigma, St. Louis, Mo.) as the chromagen; Harris' hematoxylin was used as a counterstain. Sections were examined with a light microscope, and the antibody staining patterns were scored in a semiquantitative fashion.

Negative controls consisted of NS-1 culture supernatant or monoclonal antibodies of appropriate immunoglobulin class and subclass not reactive with ovarian tissue sections.

Results

A total of 98 specimens from 57 patients (stage I, 1; stage II, 7; stage III, 45; stage IV, 4) with epithelial cancers of the ovary were examined. These included tumor from 32 primary and 66 metastatic sites. Fifty-seven specimens were obtained from 33 patients previously untreated with chemotherapy; 11 specimens from eight of these patients were available after chemotherapy. An additional 30 specimens were studied from 24 other patients after chemotherapy for whom no pretreatment tissue was available. Postchemotherapy specimens were available from 19 patients who had been treated with one or more drugs specifically associated with selection of the MDR phenotype: doxorubicin (18 patients, mean eight courses), etoposide (2 patients, mean six courses), mitoxantrone (2 patients, mean six courses), vinblastine (1 patient, seven courses), and mitomycin (1 patient, five courses). Other chemotherapeutic agents used included cisplatin, cyclophosphamide, 5-fluorouracil, and others. The distribution of tumors analyzed in this study is shown in Table I by histologic cell type together with a summary of the staining results obtained with the two anti-P-glycoprotein monoclonal antibodies.

In only four of the 57 patients (7%) did one or more of the specimens express P-glycoprotein (Table II). All four patients had stage III disease. In two patients expression was detected at approximately the same level both before and after treatment with intravenous cisplatin and cyclophosphamide (one patient) and intravenous cisplatin and cyclophosphamide followed by intraperitoneal cisplatin (one patient). One patient was

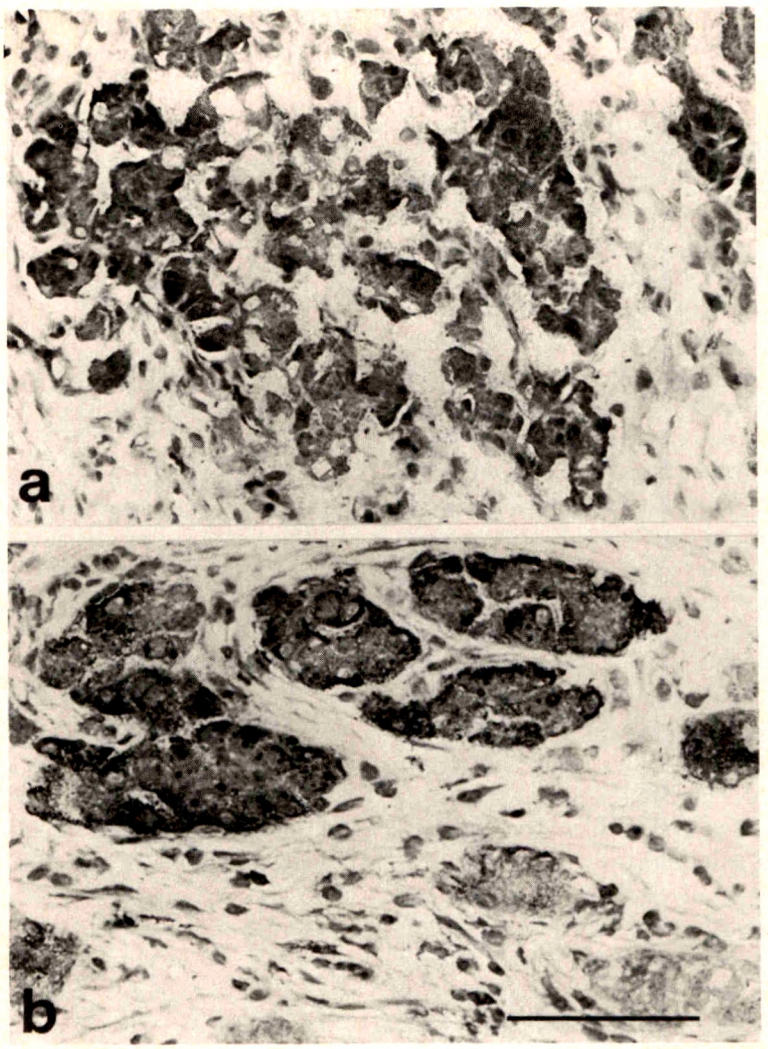


Fig. 1. Ovarian adenocarcinoma from patient No. 1 stained with monoclonal antibody C219 illustrating an apical membrane pattern of P-glycoprotein expression in the ovary **(A)** before chemotherapy and a colon nodule **(B)** after cyclophosphamide and cisplatin chemotherapy. Note weak heterogeneous pattern of staining in some but not all tumor cell islets **(B).** *Bar* = 100 μm.

considered clinically drug resistant; the other was not. Specimens from two other patients expressed P-glycoprotein at a high level in specimens obtained after treatment with the same drugs; specimens before treatment were not available. Disease in one of these patients was considered chemotherapy-resistant. A total of six specimens were examined from these four patients; expression of P-glycoprotein and expression of the other cell surface antigens studied did not vary among a given patient's specimens. No differences were observed between monoclonal antibody C219 and monoclonal antibody JSB-1 in the pattern of staining or in the number of positive specimens. Fig. 1 illustrates the staining pattern of a serous ovarian carcinoma from patient No. 1 before and after chemotherapy with mAbC219. Although the majority of the tumor cell islets stained with both antibodies, some islets were negative or showed heterogeneous expression with staining of individual tumor cells. The clinical characteristics of the patients with positive stains and the antigenic phenotypes of their tumors as determined by our panel of monoclonal antibodies are summarized in Table II. The tumor specimens from all four patients strongly expressed the antigens MH99, MW162, MX35, MW207, and CA125, which are characteristic of epithelial ovarian cancers and some other carcinomas. Specimens from three of the four patients also expressed MT334, a more restricted epithelial cell

marker that was detected in tumors from only 13 of the other 53 patients examined.

Comment

Use of the murine monoclonal antibodies C219 and JSB1, which detect different internal epitopes of the P-glycoprotein molecule, identified expression of P-glycoprotein in the tumors of only four of 57 (7%) patients with ovarian cancer, despite extensive investigation of multiple specimens from primary and metastatic sites before and after chemotherapy. No quantitative difference was observed in the staining pattern between the two antibodies. This low level of expression of P-glycoprotein in ovarian cancers is consistent with smaller studies from other investigators.[6, 7] This study, the first to examine P-glycoprotein expression in paired tumor specimens from the same patients both before and after chemotherapy, was unable to document any increase in expression of P-glycoprotein as a result of exposure to chemotherapy. Other studies that did not test paired specimens have suggested that this does occur as determined by measurement of MDR1 ribonucleic acid.[6, 7] In our material specimens from two of 33 untreated patients expressed P-glycoprotein, whereas specimens from four of 32 treated patients expressed P-glycoprotein. This difference was not statistically significant. Eight patients (two expressors) tested both before and after chemotherapy showed no change in tumor reactivity to P-glycoprotein. Significantly, no expression of P-glycoprotein was found in tumors from 19 patients exposed to chemotherapeutic drugs specifically known to cause selection of the MDR phenotype in vitro. This is in contrast to the findings of Bourhis et al.[7] who observed MDR1 ribonucleic acid expression in three of 10 patients treated with doxorubicin or vincristine and therefore suggested a role for P-glycoprotein in the acquired chemoresistance of ovarian cancer.

Given the widespread distribution of P-glycoprotein in normal human tissues,[8] it is possible that methods of detection that used electrophoresis of homogenized tissue to measure MDR1 deoxyribonucleic acid, ribonucleic acid, or protein, including Southern, Northern, and Western blotting, may overestimate the extent to which tumors express the MDR1 gene, as a result of contamination of tumor specimens with normal cells expressing P-glycoprotein. Similarly, it is possible that exposure to chemotherapy of the various nonmalignant cellular elements of tumor specimens, including stromal cells and blood cells, may result in increased expression of P-glycoprotein by these cells that could be interpreted by techniques that use homogenized tissue as increased tumor cell expression. Alternatively, it has been proposed that a subpopulation of P-glycoprotein–expressing tumor cells could be obscured by negative cells with these techniques. Methods that allow a more precise determination of P-glycoprotein expression at the cellular level, such as immunohistochemistry and in situ hybridization, may be more accurate in this regard.

Table II. Antigenic phenotype in four patients with epithelial ovarian cancer expressing P-glycoprotein

Patient No.	*Prior chemotherapy*	*Cell type and grade*	*Tumor sites*
1	None	Serous, 3	Ovary
	CTX, CDDP IV, CDDP IP		Colon
2†	None	Serous, 3	Omentum
	CTX, CDDP IV		Pelvis
3†	CTX, CDDP IV, CDDP IP	Serous, 3	Colon
4	CTX, CDDP IV	Undiff, 3	Uterus

CTX, Cyclophosphamide; *CDDP,* cisplatin; *IV,* intravenous; *IP,* intraperitoneal; *Undiff,* undifferentiated; *P-GP,* P-glycoprotein; *Mabs,* monoclonal antibodies.

*Monoclonal antibody reactivity was designated as follows: + + + +, homogenous reactivity; + + +, heterogeneous reactivity with 70% to 90% cells; + +, heterogeneous reactivity with 30% to 70% cells; +, heterogeneous reactivity with 10% to 30% cells; 0, negative.

†Indicates patient considered to have clinically drug-resistant disease on the basis of assessment of response at laparotomy.

Pharmacologic reversal of multidrug resistance has been reported in vitro with a variety of agents including verapamil, trifluoperazine, reserpine, quinidine, perhexiline maleate, anthracycline and vinca alkaloid analogs, and cyclosporine.[9-13] Dalton et al.[9] recently reported finding P-glycoprotein expression on tumor cells from six of eight patients with clinically drug-resistant multiple myeloma or non-Hodgkins lymphoma and demonstrated subsequent responses to chemotherapy in three of the eight patients when verapamil was added to the chemotherapy regimen. P-glycoprotein is apparently expressed in a small number of ovarian cancers, and expression has been reported to increase after exposure to chemotherapy,[6, 7] although we did not observe this in our study. Ozols et al.[14] were unable to demonstrate potentiation of the activity of doxorubicin by verapamil in eight patients with drug-resistant ovarian cancer, although the tumors had not been shown to express P-glycoprotein. Systemic toxicity of verapamil will limit its usefulness for this purpose. In vitro reversal of multidrug resistance in a doxorubicin-resistant breast cancer cell line has been

*Monoclonal antibody reactivity**								
P-GP Mabs		*Epithelial cell antigen Mabs*						
C219	*JSB-1*	*OC125*	*MH99*	*MW162*	*MX35*	*MW207*	*MT334*	*A33*
+ + +	+ + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	0	0
+ +	+ +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	0	0
+ + +	+ + +	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ + + +	0
+ + +	+ + +	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ + + +	0
+ + +	+ + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ +	0
+ + + +	+ + +	0	+ + + +	+ + + +	+ + + +	+ + + +	+ +	0

demonstrated with clinically achievable concentrations of toremifine, a tamoxifen analog likely to be well tolerated clinically.[15]

A recent report suggests that P-glycoprotein may be expressed in a small proportion of normal ovaries.[16] Its expression in occasional ovarian adenocarcinomas, which generally are derived from the surface epithelium of the ovary, may simply represent expression of a normal tissue differentiation antigen in a malignancy arising from that normal tissue.

Some women with epithelial ovarian cancer have tumors that are primarily chemotherapy resistant, and a large proportion of the others can be expected to manifest drug resistance in the future. Despite this, only a small proportion of these tumors express P-glycoprotein. It appears from this study that for the majority of patients with epithelial cancer of the ovary, resistance to the drugs most active against this cancer is mediated through mechanisms other than expression of the MDR1 gene product.

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Large cystic granulosa cell tumor: Case report

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This is a case of a large granulosa cell tumor of the ovary. The patient was a 42-year-old, white woman, gravida 1, para 1. The family claimed that she had a "water tumor" in her abdomen. The patient was afraid of seeing a doctor. She died at home without any medical attention. During autopsy we removed approximately 20 gallons of turbid reddish brown fluid from the cystic tumor. The tumor's cystic wall and the fluid weighed approximately 77 kg (170 pounds). No metastasis was found in any other organs. (Am J Obstet Gynecol 1990;163:74-6.)

Key words: Granulosa cell tumor, ovary

A case of a large granulosa cell tumor of the ovary is described. The woman failed to seek medical attention.

Case report

A 42-year-old white woman, gravida 1, para 1, was found dead in her apartment. During the last 3 days before her death, she had not moved at all and sat in a chair clutching a baby blanket. According to the family, they, along with the patient, noticed the growth in her girth 6 months previously but she failed to seek medical attention. Her medical history was unremarkable other than "not feeling good." She was not taking any medications. When the body arrived in the Stark County Coroner's morgue, an autopsy was performed.

The physical examination showed a well-developed, well-nourished white woman. The breasts were well developed and normal axillary and pubic hair was present. The upper extremities did not show pitting edema; however, the lower legs and feet revealed pitting edema (4+). The abdomen was extensively distended with the girth at the umbilicus measuring 168 cm (66 inches) (Fig. 1). The external genitalia were unremarkable. The skin on the back and abdomen showed irritated and eczematous changes.

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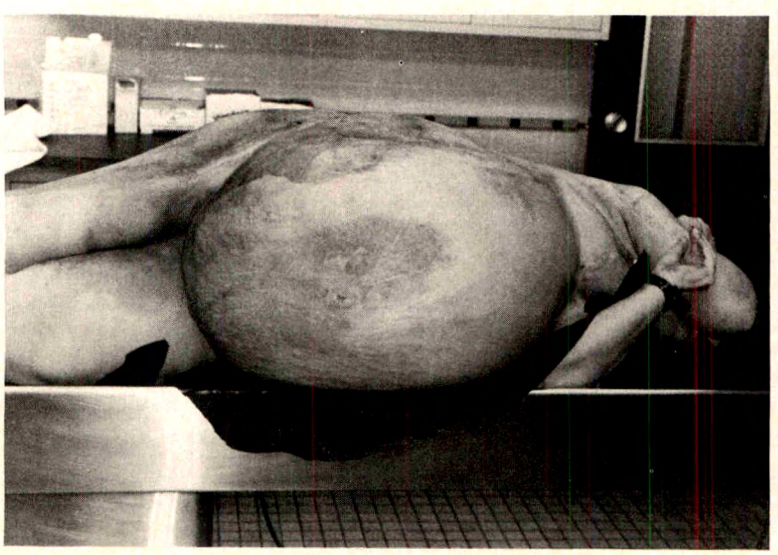


Fig. 1. Girth was 168 cm (66 inches), and approximately 76 L (20 gallons) of fluid was removed.

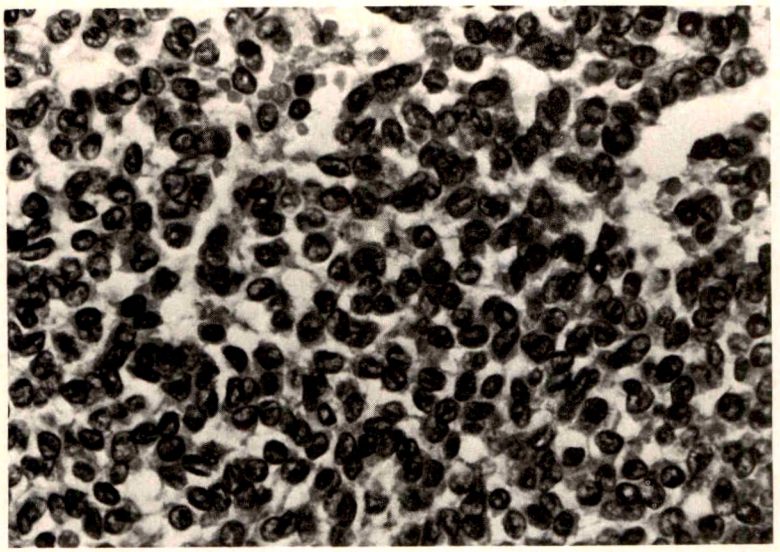


Fig. 2. Tumor cells have scanty cytoplasm. Nuclei are oval with prominent nuclear grooves (coffee bean–shaped nuclei). (Original magnification ×400.)

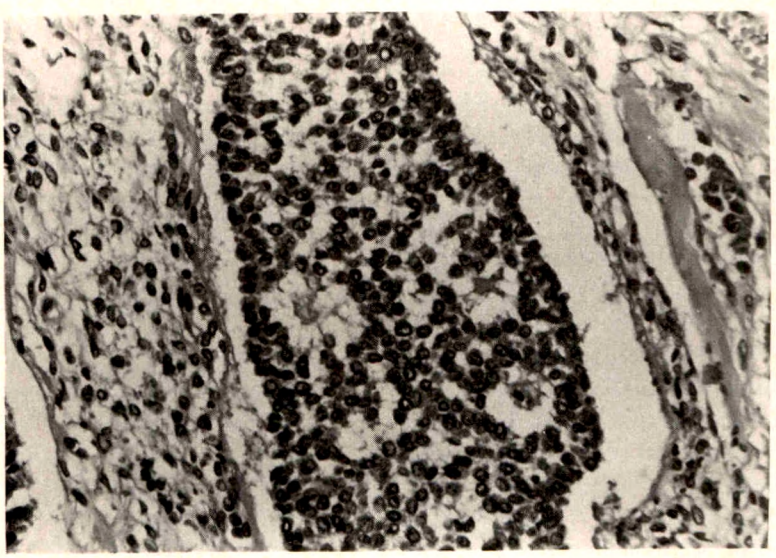


Fig. 3. Several Call-Exnar bodies are present. (Original magnification ×200.)

Before we opened the abdomen, the fluid was drained. There was approximately 76 L (20 gallons) of turbid reddish brown fluid. On opening the abdomen virtually the entire abdominal cavity and part of the pleural cavity were replaced by a cystic tumor mass. The inner surface of the cyst wall was necrotic, hemorrhagic, and irregular. The cyst measured approximately 56 cm (22 inches) in greatest diameter. The cyst wall measured 1 to 2 cm in thickness. The outer surface of the cyst was pink and glistening. The heart, lungs, and other organs were displaced and compressed by the large ovarian cystic tumor. The mass arose from the right ovary. The left ovary and uterus were within normal limits.

Histologically, the wall of the ovary and cyst showed oval hyperchromatic cells with scanty cytoplasm. Many cells showed nuclear grooves (coffee bean–shaped nucleus) (Fig. 2). Numerous Call-Exner bodies were present (Fig. 3). Sections from the endometrium showed adenomatous hyperplasia with focal cystic changes. The

tumor was probably functional because of the presence of adenomatous hyperplasia with focal cystic changes in the uterus. No other organs showed evidence of metastasis.

Comment

In 1939, Drs. Dockerty and McCartney[1] reported on large granulosa cell tumor of the ovary, which weighed approximately 35 pounds. In 1971, Drs. Robertson and Miller[2] reported on a massive cystic granulosa-theca cell tumor that weighed approximately 150 pounds. We describe almost the same size of tumor; however, ours is slightly larger than the most recent case. We believe our tumor is the largest recorded tumor of the same type.

We are grateful to Brenda L. Sherrod for providing assistance.

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5-Fluorouracil exposure during the period of conception: Report on two cases

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Two patients who were administered topical vaginal 5-fluorouracil for human papilloma virus lesions became pregnant during treatment. The outcomes in both cases were healthy with normal developmental landmarks at 6 months of age. This experience highlights the potential for a positive outcome. (Am J Obstet Gynecol 1990;163:76-7.)

Key words: 5-Fluorouracil, periconceptual exposure

The incidence of lesions associated with human papillomavirus has increased dramatically in the past two decades. The treatment of these viral lesions has proved to be associated with recurrence in 10% to 35% of cases. Consequently, adjuvant or prophylactic use of 5-fluorouracil (5-FU) intravaginal therapy is becoming a widely accepted protocol. An obvious sequela of this new protocol is unexpected periconceptual exposure of the developing embryo to 5-FU, an antideoxyribonucleic acid chemotherapeutic agent. We present two cases of exposure during this period that resulted in two healthy, thriving infants.

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6/1/20000

Case report

Patient 1. A 26-year-old gravida 3, para 1-0-1-1 patient was first diagnosed and treated for genital condyloma at age 19 years. She had a history of regular 28-day cycles. Conization of the cervix was performed by laser vaporization after colposcopic examination and an abnormal biopsy specimen was obtained. The patient had daily application of approximately 65 mg of 5% 5-FU cream (Efudex, Roche Laboratories) to the vagina and cervix on cycle days 15, 16, and 17 for an estimated total of 185 mg of 5-FU. On approximately cycle day 31, the patient had positive results for β-human chorionic gonadotropin. By the last menstrual period and ultrasonographic evaluation, the embryo was exposed between conception cycle day 15 and cycle day 21. Level II ultrasonography at 21.1 weeks' gestation revealed a normal anatomic survey. The maternal serum α-fetoprotein level was 48 ng/ml or 1.6 multiples of the median. The patient was delivered by repeat cesarean section at term of a 3720 gm male infant with Apgar scores of 9 at 1 and 5 minutes. No anomalies were noted by a consulting pediatrician. The infant's developmental milestones have been uneventful at 6 months of age.

Patient 2. A 21-year-old gravida 1, para 0 patient was diagnosed with systemic lupus erythematosus at the age of 18 years. At that time the patient was given hydroxychloroquine sulfate and prednisone. At age 19 years, the patient had a colposcopically directed biopsy specimen diagnosis of cervical intraepithelial neoplasia, grade 2, and human papillomavirus infection. Her cycles at that time were regular and 28 to 30 days in length. After laser conization the patient received about 65 mg daily of adjuvant 5-FU intravaginal therapy on cycle days 18, 19, 20, and 21 for an appropriate total of 260 mg of 5-FU. On the basis of ultrasonographic evaluation and last menstrual period, exposure would have occurred at the time of conception. An ultrasonographic examination at 18.5 weeks' gestation revealed a normal anatomic survey. Although there was no evidence that a genetic amniocentesis would be informative, the patient elected to have this procedure performed. The results were: (1) 46,XY karyotype with no structural abnormality of the chromosomes; and (2) fetal α-fetoprotein = 9.4 μg/ml, which is within 2.3 multiples of the mean.

The patient had a normal vaginal delivery at term of a 3724 gm male infant with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. This infant had normal examination results at birth and normal developmental milestones at 21 months of age, as evaluated by a pediatric consultant.

Comment

The treatment of human papillomavirus–associated lesions is troublesome and lengthy for many women. Sillman et al. found incorporation of 5-FU maintenance therapy to be highly successful. Conception exposure incidence may be on the rise. Two cases of 5-FU exposure in pregnancy have been reported to date. Stephens et al.[1] reported multiple congenital anomalies in a fetus exposed to 5-FU during the first trimester and suggested that 5-FU may be a teratogenic agent. Stadler and Knowles[2] reported a case of intrauterine exposure to 5-FU at approximately 22 to 23 weeks' gestation that was subsequently interpreted as a case of neonatal intoxication.

It has been reported that 6% of a topically applied dose of 5-FU penetrates the skin in 24 hours. Diseased skin has been found to absorb approximately 15 to 75 times greater quantities of topically applied 5-FU than does normal skin. No evaluation with regard to vaginal absorption of 5-FU has been performed to our knowledge. Several investigators have shown that inert particles are easily and spontaneously transported from the vagina through the genital tract to the ovaries. Peripheral measurement of 5-FU would not be an accurate reflection of the true embryo exposure in the uterine or tubal lumen. Therefore the pharmacokinetic data outlined above may not be pertinent to vaginal 5-FU exposure, especially in the periconceptual period.

The preimplantation period is considered one when the embryo is invulnerable. This relates to the fact that in general the embryo will not be exposed to agents ingested by the mother until implantation. However, in the case of intravaginal 5-FU it is most likely that the embryo itself is in the fallopian tube and uterus at concentrations that exceed those circulating in the mother. The exact level cannot be quantitated.

We retain two possible explanations for the positive outcomes described here. One is that indeed 5-FU is a potent teratogenic agent. If the early embryo is affected, then a spontaneous loss will occur; otherwise the pregnancy will continue without associated complications. This all-or-none effect of early exposure to teratogenic agents is well described. Another possibility is that 5-FU exerts little or no teratogenic effect. It is likely that an uneventful ongoing pregnancy after periconceptual exposure will not display any adverse effects.

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Detection of fetal blood contamination by amniotic fluid obtained during cordocentesis

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When a fetal blood sample is obtained by cordocentesis it is important to know whether the sample is diluted with amniotic fluid. This study was designed to assess whether contaminated fetal blood samples could be discriminated from noncontaminated ones by the ferning test, and if so what is the minimum dilution ratio of amniotic fluid/fetal blood that is detectable. Fetal blood samples were diluted with amniotic fluid and were tested for ferning under the microscope after the plasma was separated from the cells. At a dilution ratio of 0.2 ml of amniotic fluid to 1 ml of fetal blood, 30% of the samples tested positive for ferning. A rate of 100% detection of ferning was achieved at a dilution ratio of 0.6:1. In conclusion, screening fetal blood samples for ferning can detect amniotic fluid contamination. The sensitivity of the test for ferning depends on the dilution ratio. The test cannot assess how much amniotic fluid was added to the blood sample. (AM J OBSTET GYNECOL 1990;163:78-80.)

Key words: Cordocentesis, fetal blood sampling, amniotic fluid contamination

Percutaneous umbilical blood sampling is gaining popularity as a method to test fetal blood samples for various clinical indications.[1] Some of the tests routinely done on fetal blood include the determination of fetal hemoglobin, hematocrit level, and other blood indices.[2] Once the needle is placed inside the umbilical artery or vein and the fetal blood sample is withdrawn, the tip of the needle may dislodge from the fetal vessel and amniotic fluid may contaminate the fetal blood sample. It is of utmost importance to know whether the fetal sample is diluted with amniotic fluid.

The following in vitro study was designed to test whether it is possible to detect amniotic fluid contamination of a fetal blood sample by the ferning test and if so, what is the minimum amniotic fluid/fetal blood dilution ratio that can be detected.

Material and methods

Amniotic fluid samples were collected after artificial rupture of the membranes on patients in active labor. We were careful not to use samples in which the amniotic fluid was grossly contaminated by maternal or fetal blood. After the neonate was delivered the cord was milked to obtain a fetal blood sample. A glass capillary was filled with the fetal blood and was centrifuged at 7000 rpm for 3 minutes to separate the serum from the cells. The hematocrit level of the sample was then determined and the plasma was spread on a glass slide and air dried. The sample was checked under the microscope for evidence of ferning.

The amniotic fluid was checked for evidence of ferning. After one drop was spread on a glass slide it was dried and checked with the microscope for ferning.

A given volume of the fetal blood sample was then diluted with the amniotic fluid starting with a dilution ratio of 0.1 ml of amniotic fluid to 1 ml of fetal blood. The dilution ratio was increased by increments of 0.1 ml up to a ratio of 1:1 and then a dilution of 2:1 was finally tested.

The diluted fetal blood samples were centrifuged at 7000 rpm for 3 minutes to separate the cells and the plasma. The plasma was spread on a glass slide, dried for 1 minute, and then examined under a microscope for evidence of ferning.

Results

A total of 10 fetal blood samples from 10 newborns were included in the study. The initial hematocrit level ranged from 44% to 58% (mean, 49.3% ± 7.8 SD).

None of the undiluted fetal blood samples tested positive for ferning under the microscope.

Table I presents the results of all fetal blood samples studied in the different dilution ratios. At a dilution ratio of 0.1 ml amniotic fluid to 1 ml fetal blood, only one sample showed evidence of atypical ferning. With increasing dilution ratios the number of samples that were positive for ferning increased. Even at lower ratios of 0.2:1, three of 10 samples tested positive for ferning. At a ratio of 0.4:1, 60% of the samples tested positive

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6/1/20939

Table I. Percent of fetal blood samples positive for ferning at different amniotic fluid/fetal blood dilution ratios

	Patients										
AF/FB	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*% Detected*
0:1	−	−	−	−	−	−	−	−	−	−	0
0.1:1	−	−	−	−	+	−	−	+	−	−	20*
0.2:1	+	−	+	−	−	−	−	−	−	+	30
0.3:1	+	−	+	−	+	−	+	+	+	−	50
0.4:1	+	+	+	+	−	+	−	+	+	+	80
0.5:1	+	+	+	+	+	+	+	−	+	+	90
0.6:1	+	+	+	+	+	+	+	+	+	+	100
0.7:1	+	+	+	+	+	+	+	+	+	+	100
0.8:1	+	+	+	+	+	+	+	+	+	+	100
0.9:1	+	+	+	+	+	+	+	+	+	+	100
1:1	+	+	+	+	+	+	+	+	+	+	100
2:1	+	+	+	+	+	+	+	+	+	+	100

AF, Amniotic fluid; *FB*, fetal blood; −, negative for ferning; +, positive for ferning.
*Atypical ferning.

for ferning. At a dilution ratio of 0.6:1 all 10 samples tested positive for ferning.

Comment

The method proposed by us to determine amniotic fluid contamination of the fetal blood sample is based on the well known fact that amniotic fluid tests positive for ferning. The amniotic fluid forms an arborization (ferning) pattern when smeared on a clean slide and allowed to air dry. The phenomenon of ferning was first reported by Kardos and Tamasi.[3] This method has been used for years to detect rupture of the membranes. The reliability and utility of ferning have been confirmed by several reports.[4-7] On the other hand, fetal blood tests negative for ferning. Reece et al.[5] conducted an in vitro study to assess the effects of blood and meconium at various dilutions on the fern test. They concluded that the fern test was unaffected by meconium at any concentration and by blood at dilutions of ≥1:10. When blood and amniotic fluid were mixed in equal amounts, ferning was not present. It is very unlikely that maternal blood will be mixed with the fetal blood sample once the tip of the needle is placed in the umbilical vessel. Even if sufficient volume of maternal blood will find its way into the syringe, this would be identified by the Apt test or by testing the mean corpuscular volume of the blood sample.

The crystallization of the amniotic fluid, which is necessary for production of fern, or arborized pattern, is dependent on the concentration of electrolytes, principally sodium chloride, in the fluid. In general, a concentration of sodium chloride of 1% is required for the full development of a fern pattern; below that concentration either a beaded pattern or atypical incomplete arborization is seen. Theoretically any of the body fluids can form ferning including the perspiration from fingerprints, and this was reported to account for false-positive findings.[8]

We speculated that if fetal blood and amniotic fluid were mixed together we could detect the contamination of the fetal blood sample with amniotic fluid. Our results show two cases of atypical ferning at a diluton of 0.1:1. This atypical fern resulted from the fact that the sodium chloride concentration in the solution was too low to form typical ferning. However, at a dilution ratio of 0.2:1, 30% of the samples tested positive for ferning. At a dilution of 0.6:1 all samples tested positive for ferning. Whereas the specificity of the proposed test is 100% the sensitivity depends on the dilution ratio. At very low dilution ratios the sensitivity is only 30%. The sensitivity increased to 90% at a ratio of 0.5:1 and 100% at a ratio of 0.6:1. Therefore the proposed test may result in a false-negative result if the dilution is <0.6:1. The lower the dilution of the blood sample, the higher the rate of false-negative reading.

In our institution cordocentesis has been performed under a research protocol for the past 2 years. Fetal blood sampling to determine fetal hemoglobin and hematocrit level is the most common reason to perform the procedure. Regardless of the clinical indication for the procedure, all samples obtained by this procedure are tested for hemoglobin and hematocrit levels. Since the test was introduced in our fetal diagnostic unit three blood samples of 47 (6.4%) tested positive for ferns and the samples were repeated.

When the procedure is indicated in the presence of hemolytic disease, idiopathic thrombocytopenia purpura, fetal hydrops, and twin-to-twin transfusion, it is of the utmost importance to know whether the blood sample obtained was diluted by amniotic fluid. In cases of fetal anemia the result may determine whether there is an indication for an intrauterine fetal blood trans-

fusion. Once a decision is made to transfuse a fetus, the volume of blood transfused depends on the initial fetal hemoglobin level. If for any reason the fetal blood sample was diluted by amniotic fluid, the result will be falsely low, directly depending on how much amniotic fluid was accidently aspirated into the sampling syringe. If the result is too low, too much blood may be transfused into the fetus. Overtransfusion of the fetus could potentially result in fetal cardiovascular compromise, especially in a hydropic or severely stressed fetus.

One of the potential ways to overcome this problem is to look at the result of the other fetal cells counted (i.e., platelets and white blood cells). However, the range of these results may vary significantly from one fetus to another and one can never tell with certainty on the basis of cell counts whether small quantities of amniotic fluid were aspirated into the syringe. Only when the fetal white blood cell or platelet count is abnormally low without any apparent cause would one suspect that the fetal sample is diluted with amniotic fluid. The other way to make certain that the tip of the needle is in place is to flash the fetal vessel with saline solution after aspiration to be certain of placement. If after doing so there is uncertainty as to the location of the needle tip, we recommend the fern test.

In conclusion, amniotic fluid contamination of fetal blood sample may be detected if the sample is screened for ferning. The detection of ferning naturally cannot identify the dilution ratio of amniotic fluid to fetal blood hence, the true fetal blood hemoglobin cannot be determined. The fern test is an option that can be used as an aid in the determination of the presence of amniotic fluid in fetal blood samples.

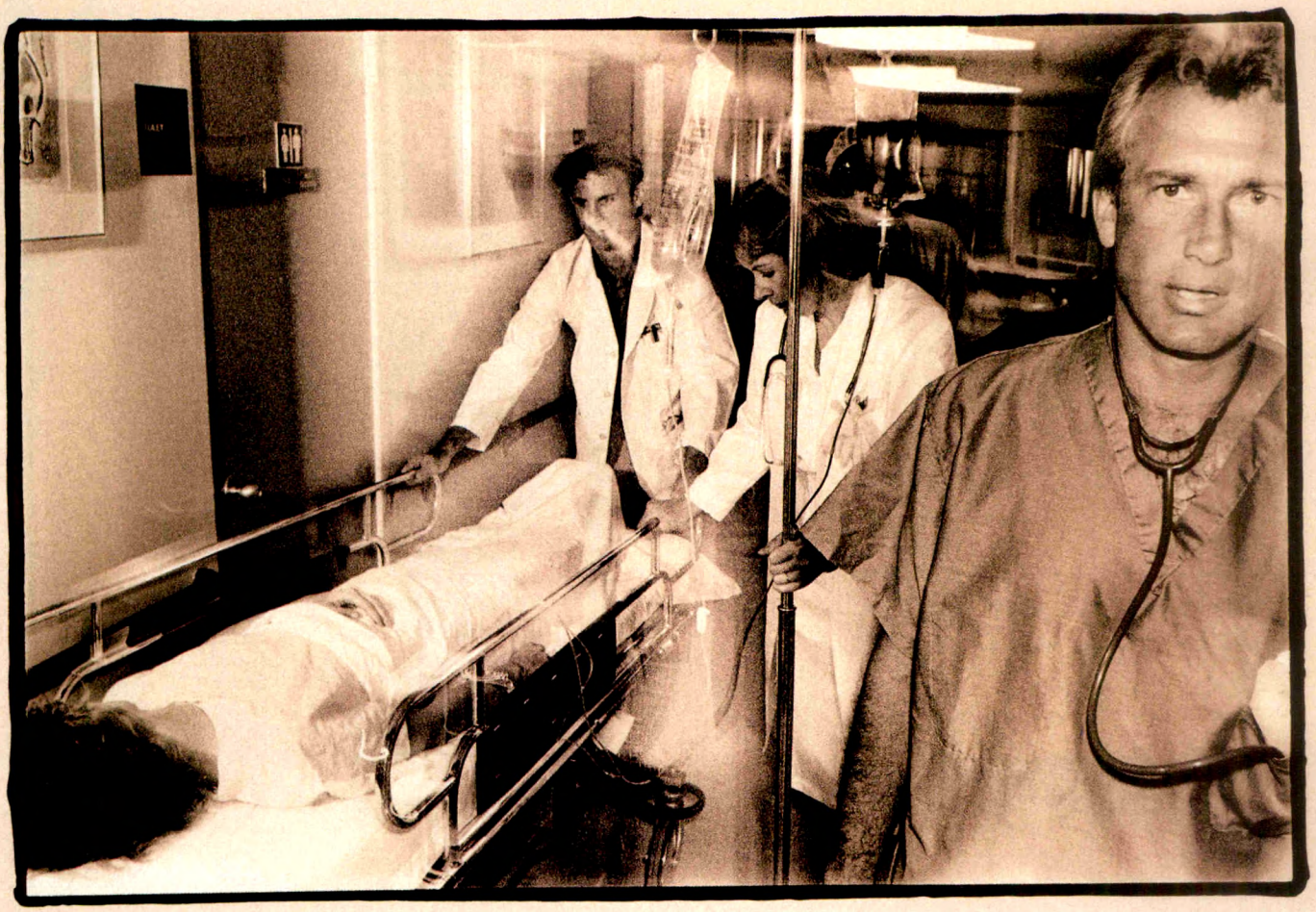
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INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*

Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported:

Local Adverse Reactions

Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.

Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.

Blood Chemistry: Decreased serum albumin and total proteins.

Renal: Increased BUN and creatinine.

Urinalysis: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN:

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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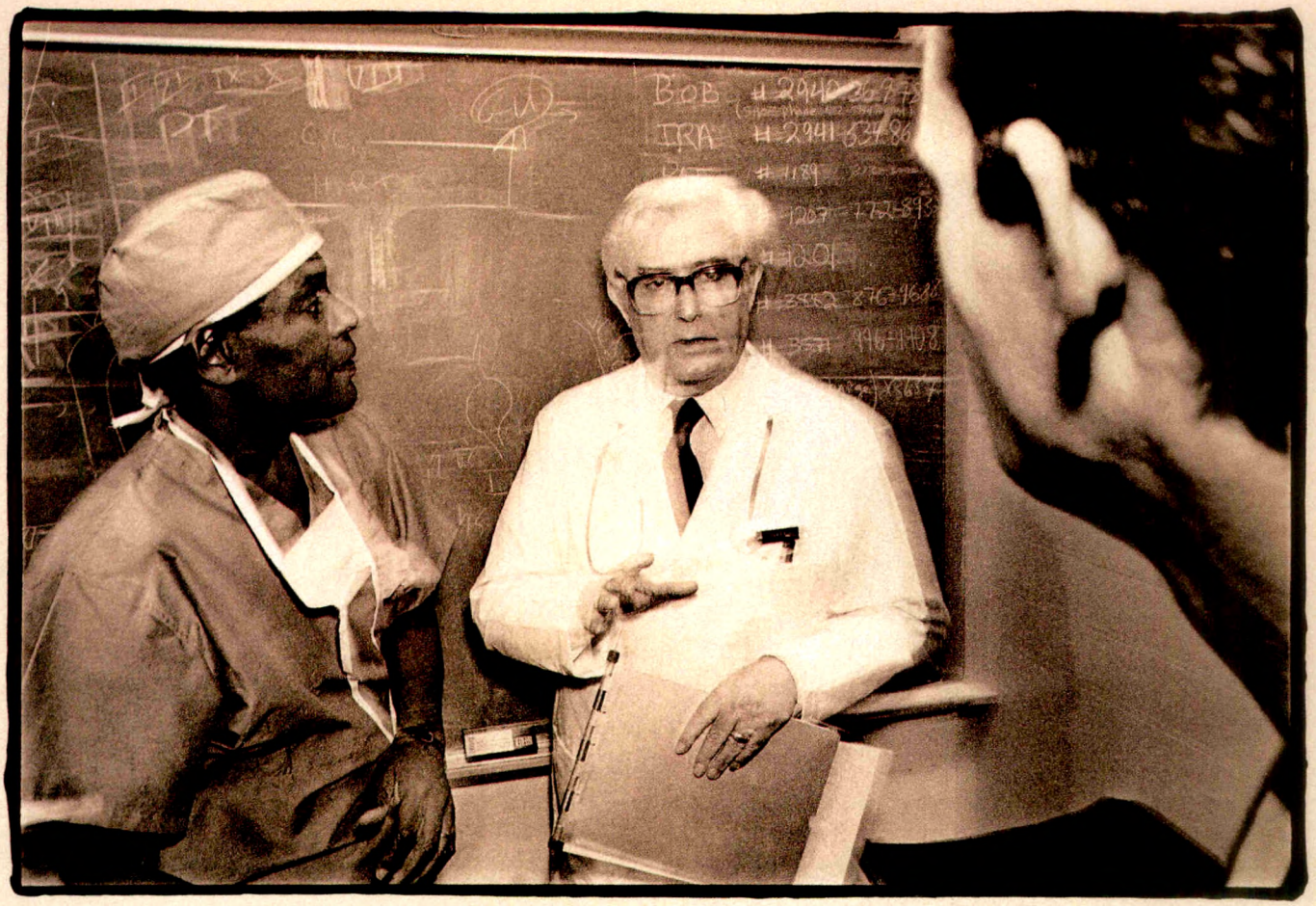
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INDICATIONS AND USAGE
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.* and *Acinetobacter calcoaceticus*.*
Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.
CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.
WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.
PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
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Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.
ADVERSE REACTIONS
UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%
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The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.
Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).
Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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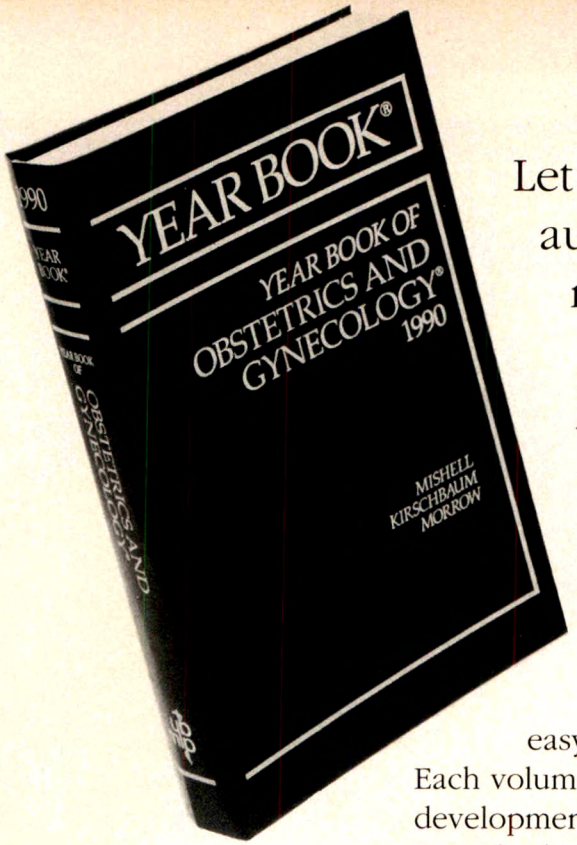
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Comparisons of glycosylated and nonglycosylated amniotic fluid prolactins in normal second- and third-trimester pregnancies

John McCoshen, PhD,[a] Eva Patalas, BSc(Med),[a] Edith Markoff, PhD,[b] David Lee, BSc,[b] and Yang Ming, MD[a]

Winnipeg, Manitoba, Canada, and La Jolla, California

Prolactins in glycosylated and nonglycosylated form were isolated from 218 second- and third-trimester amniotic fluid samples by sodium dodecyl sulfate–polyacrylamide gel electrophoresis, electrotransferred to nitrocellulose paper, and probed with anti–human prolactin serum and protein A labeled with iodine 125. The glycosylated and nonglycosylated prolactin bands were exposed by autoradiography. The bands were analyzed by densitometry, and the ratio of glycosylated to total (glycosylated + nonglycosylated) prolactin was calculated (glycosylated/total ratio) and compared with matched prolactin radioimmunoassay measurements. Both radioimmunoassay-measured and nonglycosylated prolactin decreased from the second to the third trimester whereas glycosylated prolactin concentrations remained unchanged. Concomitantly, glycosylated/total prolactin ratios increased significantly ($p < 0.001$). The correlation of radioimmunoassay-measured prolactin was closer to nonglycosylated prolactin ($r^2 = 0.32$, $p = 0.00001$) than to glycosylated prolactin ($r^2 = 0.02$, $p = 0.06$). We suggest that the proportion of amniotic fluid glycosylated prolactin increases with length of gestation and that glycosylation of prolactin is inversely related to total prolactin secretion. Furthermore, prolactin's immunoreactivity correlated more closely to the nonglycosylated-prolactin variant, suggesting that radioimmunoassay of prolactin poorly recognizes the glycosylated prolactin form. (Am J Obstet Gynecol 1990;163:81-5.)

Key words: Prolactin, glycosylation, amniotic fluid

Amniotic fluid prolactin (PRL) reaches peak levels in the second trimester of pregnancy and then decreases about fivefold by the third trimester.[1, 2] It originates in decidua and reaches the amniotic fluid by translocation across the fetal membranes.[3, 4] Two major molecular variants of PRL include the 23,000 molecular weight nonglycosylated moiety and a 25,000 molecular weight glycosylated form. Both are secreted by the pituitary gland and decidua and are normally present in the sera of men and nonpregnant women.[5-10] However, during pregnancy, when PRL concentrations increase, glycosylated PRL is particularly apparent.[6-8]

The profile of immunoassayable PRL in amniotic fluid is well delineated.[1-3] However, we know little concerning the glycosylated PRL variant and its physiologic significance in pregnancy. Radioimmunoassay (RIA) may detect only ≤30% of glycosylated PRL and, depending on the method used to measure bioactivity, purified glycosylated PRL is reported to have between 0% and 80% of the activity of nonglycosylated PRL.[9-12] Furthermore, with a specific antibody for glycosylated PRL not yet available, RIA measurements of PRL cannot discrminate between the glycosylated and nonglycosylated forms.[13]

In this study alternative analytic methods were used in conjunction with RIA, toward understanding the relationship between heterologous prolactins within the amniotic fluid compartment during the second and third trimesters of normal pregnancy.

Material and methods

Single amniotic fluid samples were obtained from the Fetal Assessment Unit and the Section of Clinical Genetics, University of Manitoba; these samples had been obtained by amniocentesis from 218 women who were subsequently proved to have genetically normal pregnancies and who had clinically normal pregnancy outcomes. Second-trimester amniotic fluid samples ($n = 194$) were obtained for genetic reasons, and third-trimester fluid samples ($n = 24$) were obtained either for assessment of fetal lung maturity ($n = 10$) or at the

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time of elective repeat cesarean section ($n = 14$). The study was approved before its commencement by the University of Manitoba Faculty Committee on the Use of Human Subjects in Research. The samples of fluid were stored at −20° C until assayed. Before assay, all samples were centrifuged to remove particulate matter. Subsequent to data collection, patient's charts were reviewed and the results of gestational age, karyotype, fetal assessment, and pregnancy outcome were recorded. The gestational age was determined at the time of amniocentesis by real-time ultrasonography and by calculation of the date of the last normal menstrual period.

RIA. The concentrations of PRL in amniotic fluid were measured in duplicate by RIA with a human PRL RIA kit from the National Institutes of Health. Intraassay and interassay variations were 6.8% and 10.6%, respectively.

Analysis of glycosylated and nonglycosylated PRL. To visualize glycosylated and nonglycosylated PRL as independent variants, samples of amniotic fluid were subjected to sodium dodecyl sulfate–polyacrylamide gel electrophoresis and immunoblot analysis as previously described.[8] Briefly, 10 μl aliquots of amniotic fluid were run on sodium dodecyl sulfate–polyacrylamide gel electrophoresis, electrotransferred to nitrocellulose paper, and probed with SB-3 anti–human PRL serum (generously supplied by Dr. S. Baxi, the Whittier Institute) and protein A. The bands were exposed by autoradiography. The measurements of glycosylated and nonglycosylated PRL levels were achieved by densitometric analysis of the autoradiographs. The positions of each PRL band were scanned in triplicate in each lane, and the mean density values were used to estimate the relative concentration in nondimensional units. Subsequently, the ratio of glycosylated to total PRL (glycosylated PRL + nonglycosylated PRL) was calculated for each lane and expressed as the glycosylated/total ratio. The interassay variation was determined from the glycosylated/total ratios in those lanes containing the purified glycosylated and nonglycosylated PRL standards ($n = 27$, mean = 0.156 ± 0.012 SD) and calculated to be 12.8%.

Statistical analysis. All data were analyzed according to gestational age and/or trimester. Statistical analysis included a parametric general linear model analysis of variance, the nonparametric Kruskal-Wallis test for group means, and simple and multiple regression analysis.

Results

A summary of the number of amniotic fluid samples obtained from each gestational age studied along with mean PRL concentrations is presented in Table I. Mean (±SEM) gestational ages of second- and third-trimester cases were 15.6 ± 0.1 and 38.2 ± 0.2 weeks, respectively. Peak levels of RIA PRL occurred at weeks 16 and 17. Mean (±SEM) RIA PRL concentrations (nanograms per milliliter) were 2766 ± 135 in the second trimester and 583 ± 74 in the third-trimester fluid. The distributions of the 23,000 nonglycosylated and 25,000 glycosylated PRL densities over gestational age are displayed in Fig. 1. As with the RIA PRL measurements, the summed nonglycosylated + glycosylated PRL densities reached peak levels over the sixteenth and seventeenth weeks and declined thereafter (data not shown). The nonglycosylated PRL–specific densities were highest during the same gestational ages while glycosylated PRL densities displayed little variation throughout gestation. Statistical analysis of these data revealed that RIA PRL, nonglycosylated + glycosylated PRL, and nonglycosylated PRL decreased significantly between trimesters, but glycosylated PRL did not (Table II); that is, the glycosylated PRL content failed to change significantly over gestational age or between trimesters. At the same time the relative proportion of glycosylated PRL to total (nonglycosylated + glycosylated) PRL, i.e., the glycosylated/total ratio, increased significantly as gestation progressed (Fig. 2). This necessarily resulted from the progressive decline in nonglycosylated PRL between the second and third trimesters accompanied by no significant change in glycosylated PRL over gestational age.

The comparison between RIA PRL measurements and glycosylated/total ratios is also represented in Fig. 2. The range of glycosylated/total ratios was 0.05 to 0.42. Correlation of RIA PRL to the glycosylated/total ratio was inverse ($r = -0.62, r^2 = 0.39$) and significant ($p = 0.02$). Thus high PRL concentrations appear to possess a proportionately lower glycosylated PRL component, suggesting that PRL heterogeneity is variable and concentration-dependent. Multiple regression analysis of RIA PRL concentrations versus nonglycosylated and glycosylated PRL had partial R^2 coefficients of 0.32 and 0.02, respectively, with probabilities of $p = 0.00001$ and $p = 0.06$. This indicated that RIA PRL measurements were more closely associated with the 23,000 nonglycosylated PRL form than with the 25,000 glycosylated PRL variant.

Comment

The profile of amniotic fluid PRL concentrations, as measured by RIA, was similar to that reported in other studies.[1, 2, 14] We found peak concentrations of immunoassayable PRL during the sixteenth to seventeenth weeks of gestation that subsequently declined approximately fivefold by the third trimester. In addition to PRL RIA, two major PRL variants were measured, including a 23,000 nonglycosylated PRL form and a

Table I. Number of amniotic fluid samples at each gestational age and mean (±SEM) PRL concentrations as determined by RIA

Gestational age (wk)	*No. of cases*	*PRL concentration (ng/ml)*			
		Mean	*SEM**	*Median*	*Range*
Second trimester					
14	11	1656	381	1350	320-4040
15	94	2484	178	2130	242-8600
16	68	3326	245	2640	500-8960
17	12	3155	598	2945	580-7220
18	3	1201	371	1400	482-1720
19	6	2863	714	2620	620-5820
Subtotal	194	2766	135	2270	
Third trimester					
36	3	697	143	715	440-935
37	3	458	140	364	275-735
38	4	762	124	713	515-1108
39	14	531	77	485	199-1390
Subtotal	24	583	74	518	
Total cases	218				

Medians and ranges of PRL determinations at each gestational age also are shown.

Table II. Statistical summary of nonparametric analysis (Kruskal-Wallis test) by trimester and gestational age of amniotic fluid PRL RIA results, densities of PRL forms, and glycosylated/total ratios.

PRL	*Trimester*		*Gestational age*	
	t Value	*p Value*	*t Value*	*p Value*
RIA	47.7	<0.001	61.7	<0.001
N + G	22.4	<0.001	33.7	<0.001
Nonglycosylated	27.2	<0.001	38.2	<0.001
Glycosylated	1.4	0.23*	14.1	0.12*
G/T ratio	26.1	<0.001	35.8	<0.001

N + G, Nonglycosylated plus glycosylated PRL, *G/T ratio,* ratio of glycosylated to total PRL. *t, t* statistic, *p,* probability value.
*Not significant.

25,000 glycosylated variant that were assessed by densitometry. For each amniotic fluid sample the nonglycosylated and glycosylated PRL values were summed and a profile of calculated total PRL was compared to the values obtained by RIA. Both measurements produced similar profiles that were significantly correlated. However, segregation of the densitometry results revealed that RIA PRL values were more closely associated with the nonglycosylated PRL form than with the glycosylated PRL variant. Furthermore, while there was a significant decrease in both RIA and nonglycosylated PRL in the third trimester, there was no significant change in glycosylated PRL over the gestational ages or between trimesters. These data suggest that the RIA used is more sensitive to the nonglycosylated form than to the glycosylated variant. Furthermore, the results also may indicate that, on a unit volume basis, glycosylated PRL secretion into the amniotic fluid is in a relatively steady state throughout pregnancy. However, considering that there is a progressive increase in amniotic fluid volume between the second and third trimesters, total secretion of the nonglycosylated PRL variant may be in a steady state while that of glycosylated PRL increases. Alternatively, PRL glycosylation and/or deglycosylation may occur subsequent to PRL synthesis, or clearance rates may differ between the two forms.

Since the source of amniotic fluid PRL is the decidual lining of the uterus,[3, 4] the appearance of glycosylated PRL in amniotic fluid suggests that it too is a decidual product that gains access to the fluid cavity by transport across the reflected fetal membranes. Production of both nonglycosylated and glycosylated PRL forms by decidual tissue has been identified.[8]

Depending on the method used, the biologic activity of purified glycosylated PRL is reported to be between 0% and 80% of the activity of purified nonglycosylated PRL.[9-12] Furthermore, while sodium dodecyl sulfate–

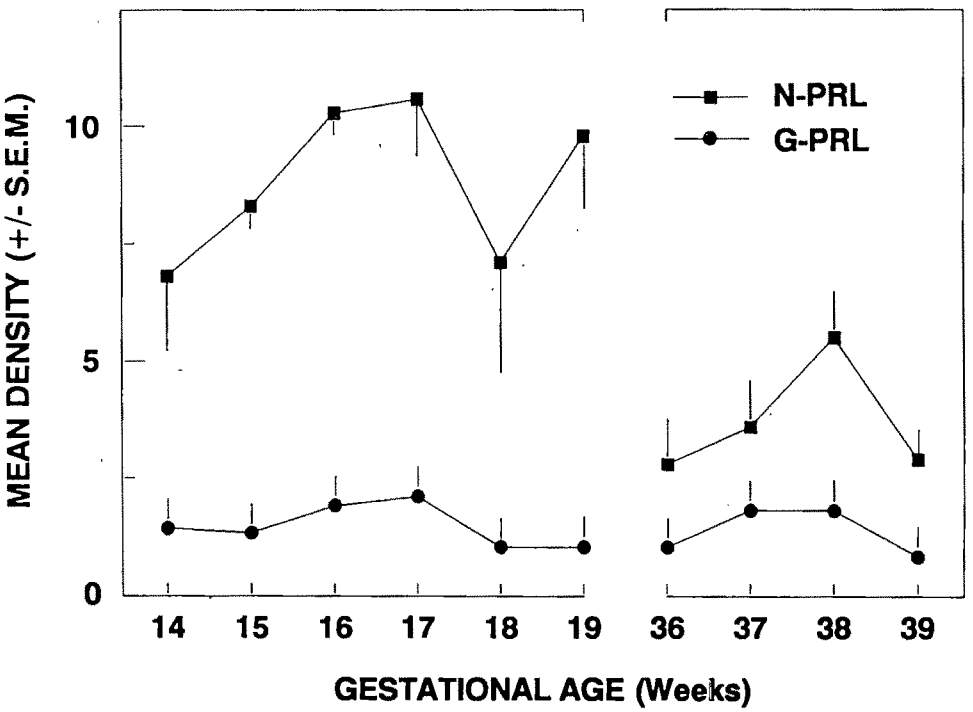


Fig. 1. Profiles of mean (±SEM) densities of nonglycosylated PRL *(N-PRL)* and glycosylated PRL *(G-PRL)* bands on immunoblot autoradiographs of normal second- and third-trimester amniotic fluid samples. *Break in border* segregates trimesters. *N-PRL*, but not *G-PRL*, significantly changed over age and between trimesters (see text and Table II for statistics).

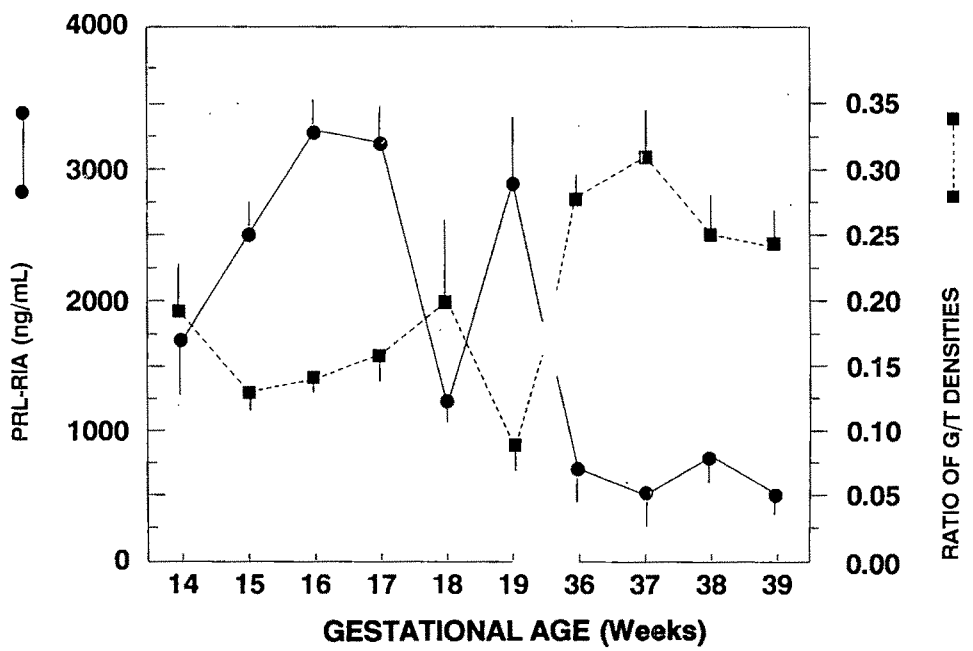


Fig. 2. Mean (±SEM) PRL RIA concentrations and ratios of glycosylated to total (glycosylated + nonglycosylated) PRL *(G/T)* in normal second- and third-trimester amniotic fluid. Break in lower border segregates trimesters. *G/T* ratio is inversely correlated ($r = -0.62, p = 0.02$) with RIA PRL concentration. RIA PRL significantly declined by third trimester while *G/T* ratio significantly increased (see text and Table II for statistics).

polyacrylamide gel electrophoresis immunoblots identified mean glycosylated PRL proportions of total PRL to be between 5% and 42%, we are still uncertain as to the total quantity of glycosylated PRL present in the amniotic fluid. RIA appears to detect only ≤30% of glycosylated PRL and is dependent on the anti–human PRL antibody used in the assay.[5, 13] We recently observed (unpublished observations), from protein stains of amniotic fluids run on sodium dodecyl sulfate–polyacrylamide gel electrophoresis, that the glycosylated PRL component of amniotic fluid actually may be in excess of the nonglycosylated form because of intense staining of the glycosylated PRL bands over those of nonglycosylated PRL, unlike that observed on immunoblots. Thus availability of an antibody specific to glycosylated PRL would allow more precise measurements of the total PRL present in both amniotic fluid and circulation.

Recently we reported that during normal pregnancy the biologic activity of amniotic fluid PRL increases between the second and third trimesters.[14, 15] In this study we found the proportion of glycosylated PRL also increased between the second and third trimesters. Since the biologic activity of glycosylated PRL in vitro is reported to be substantially less than that of the nonglycosylated PRL form,[9-12] our present findings suggest the paradox that glycosylated PRL may actually increase the overall biologic activity of amniotic fluid PRL. However, we have observed that the biologic activity of amniotic fluid PRL, as determined by the *Nb-2* lymphoma cell bioassay, may be mediated by human chorionic gonadotropin (McCoshen JA, Patalas E. Unpublished observations). Thus the biologic activity of amniotic fluid PRL may be a function of the proportion of the two major PRL variants, and specific production and activity of each variant may be under the influence of different factors.

In summary, these results identify nonglycosylated and glycosylated PRL variants in amniotic fluid. On a unit fluid-volume basis, nonglycosylated PRL paralleled PRL RIA values over time while glycosylated PRL did not. Thus the proportion of glycosylated PRL increases into the third trimester as total PRL declines. We speculate that secretion of the nonglycosylated and glycosylated PRL forms into the amniotic fluid may be controlled in part by different factors. Also, because of the poor correlation of PRL RIA results to glycosylated PRL measurements, we suggest that PRL RIA underestimates the total PRL content of amniotic fluid. Thus we speculate that the relative quantities of glycosylated and nonglycosylated PRL influence both concentration and bioactivity measurements that are important in determining the physiologic bearing of prolactin on pregnancy.

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Glucose tolerance in pregnancy: Ethnic variation and influence of body habitus

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Little is known about ethnic differences in glucose tolerance during pregnancy. In this study we examined 3366 Hispanic, Chinese, black, and non-Hispanic white women in a universal screening program for gestational diabetes mellitus. After maternal age and body mass index were controlled, Chinese women had a significantly higher serum glucose level 1 hour after 50 gm of oral glucose (134.8 ± 1.2, mean ± SE) than any of the remaining three groups. Black women had a significantly lower value (113.3 ± 1.3, mean ± SE) than either Chinese or Hispanic women (124.4 ± 0.9, mean ± SE). Results for Hispanic women and non-Hispanic white women (121.4 ± 1.6, mean ± SE) were not different. The screening glucose levels of Chinese women were substantially higher than other ethnic groups even when women with gestational diabetes were removed from the analysis, indicating that the observed differences were not solely due to a higher frequency of gestational diabetes among the Chinese. The incidence of gestational diabetes was significantly greater for Chinese (7.3%) and Hispanic (4.2%) women than for black (1.7%) and non-Hispanic white (1.6%) women. Among women who had a 3-hour glucose tolerance test, the area under the glucose curve was significantly associated with maternal age and body mass index. The demonstrated heterogeneity of glucose tolerance between ethnic groups may be of importance in determining the threshold for diabetic fetopathy, and it is possible that ethnicity-specific standards will need to be developed. (AM J OBSTET GYNECOL 1990;163:86-92.)

Key words: Glucose tolerance, ethnicity, body habitus

Gestational diabetes mellitus is associated with a variety of complications of pregnancy, including macrosomia, birth trauma, and metabolic complications of the newborn.[1, 2] Gestational diabetes mellitus also appears to be a predictor of decompensated diabetes mellitus in later life.[3] It is currently recommended that all pregnant women be screened between 26 and 32 weeks of pregnancy with a 1-hour glucose determination after administration of 50 gm of oral glucose.[4] When the serum glucose level exceeds 140 mg/dl on this glucose load test, a 3-hour oral glucose tolerance test (GTT) should be performed with 100 gm of oral glucose. In the United States the GTT is usually interpreted according to criteria established by the National Diabetes Data Group.[5] On the basis of the studies of O'Sullivan and Mahan,[6] from which this screening protocol derives, the expected incidence of gestational diabetes mellitus is approximately 2.5%.

There is substantial variation in the reported incidence of gestational diabetes mellitus. In the series summarized by Hadden,[7] the incidence varied from 0.15% to 12.3%. At least three factors contribute to this variation. First, selection of only "high-risk" patients for testing will result in loss of sensitivity and incomplete ascertainment of the incidence of gestational diabetes mellitus.[7, 8] Second, standardization of test procedures is lacking. While the 100 gm GTT has gained wide acceptance in the United States, the 75 gm oral GTT recommended by the World Health Organization[9] is more commonly used elsewhere. The WHO criteria define impaired glucose tolerance as a 2-hour plasma value for glucose ≥140 mg/dl and gestational diabetes mellitus as a 2-hour plasma value for glucose ≥200 mg/dl.[9] Paired testing by the two protocols shows that their congruence is poor; the overall agreement is only 60%, and the WHO protocol appears to be a more stringent test.[10]

Constitutional, ethnic, and racial factors may further contribute to variation in the incidence of gestational diabetes mellitus. Women who have gestational diabetes

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mellitus are known to be older and heavier than women with normal glucose tolerance,[8,11] although it is not clear to what extent the effects of age and obesity are interrelated. Reliable estimates of the incidence of gestational diabetes mellitus in many ethnic or racial groups are lacking. The study by O'Sullivan and Mahan[6] on which National Diabetes Data Group standards are based, was conducted in an urban population consisting of predominantly non-Hispanic white (60%) and black (40%) women. In that study no differences were found between the races. Merkatz et al.[12] found a higher proportion of results in the upper ranges among non-Hispanic white women than among nonwhite women, although the incidence of gestational diabetes mellitus was similar in both studies. Other examples of apparent ethnic variation exist. The Pima Indians[13] have an incidence of gestational diabetes mellitus nearly 40 times that of the population studied by O'Sullivan and Mahan[6] and 10 times that of the population studied by Merkatz et al.[12] A recent study from Hong Kong[14] found a 13% incidence of gestational diabetes mellitus by the National Diabetes Data Group criteria among Chinese women who were selected for risk factors. Although this does not represent a population-based estimate, it is far higher than the rate of gestational diabetes mellitus among women with risk factors in other reports.[7]

Our early experience with a universal glucose screening program at San Francisco General Hospital suggested that there are substantial ethnic differences in the incidence of gestational diabetes mellitus. We were also interested in examining the influence of age and maternal body habitus on glucose tolerance in pregnancy. For these reasons we undertook a prospective study of glucose tolerance in pregnancy in a mutiethnic population, using a common standard for abnormality and without selecting subjects for high-risk factors.

Material and methods

Women who enrolled for prenatal care at San Francisco General Hospital or one of its satellite clinics before completion of thirty-two weeks of pregnancy were potential candidates for this study. The hospital serves predominantly women of low socioeconomic status; fewer than 5% have private health insurance. Since April 1983 it has been our policy to perform a 50 gm glucose test (glucose load test) on all prenatal patients between 26 and 32 weeks of pregnancy. Major risk factors for gestational diabetes mellitus prompt screening at an earlier point in pregnancy, with repeat testing in the early third trimester if that test result is negative. Women who are first seen for care after 32 weeks are not routinely screened, unless major risk factors are present. Between April 1983 and May 1986 a total of 4210 women underwent screening by this protocol. This number of subjects represents approximately 60% of the hospital's total prenatal population entering the third trimester of pregnancy during that period. The major reason for failing to screen was registration for care after 32 weeks. Acceptance of screening by both providers and patients was very good; once all the satellite clinics instituted the protocol, approximately 85% of potential subjects were screened successfully. The ethnic distribution of women who were screened and those who were not was very similar.

The great majority of glucose load tests were performed by a single individual. The tests were all performed during morning clinic sessions. Initially, patients were asked to fast overnight; during the latter phases of the study this requirement was relaxed, so that the woman did not eat for 2 hours before glucose was administered. The 50 gm of oral glucose was consumed within 5 minutes under direct observation, and the patient was asked not to eat, drink, smoke, or exercise during the subsequent hour. A specimen of venous blood was collected within five minutes of 1 hour after consumption of the glucose, and the serum was separated for analysis later the same day. The concentration of glucose was determined in the hospital's clinical laboratory by a standard automated hexokinase method.

During the study period the threshold for abnormality of the glucose load test was maintained at 150 gm/dl; it has subsequently been lowered to 140 mg/dl in compliance with more recent recommendations.[4] Women with abnormal results of the glucose load test were scheduled for a 3-hour GTT. After an overnight fast, a fasting serum glucose value was obtained and a 100 gm glucose load was given orally. Samples were drawn at 1, 2, and 3 hours after ingestion. Women were asked to refrain from eating, drinking, exercise, and smoking during this period of time. The threshold for abnormality of each of these specimens was as follows: Fasting, 105 mg/dl; 1 hour, 190 mg/dl; 2 hours, 165 mg/dl; 3 hours, 145 mg/dl. The GTT result was considered normal if none of the values met or exceeded the threshold. A single abnormal value constituted a "borderline" test, while two or more abnormal values were considered diagnostic of gestational diabetes mellitus.

At the time of the glucose load test, additional data were collected for the study and abstracted onto a data sheet. Maternal height and weight at the time of the glucose load test were confirmed. Patients were characterized as obese if weight-for-height exceeded 120% of ideal, when adjusted for expected pregnancy weight gain by locally generated curves. Self-reported prepregnancy weight was recorded; however, fewer than 20% of patients actually had access to scales at home, and this value was felt to be unreliable. Maternal body

Table I. Overall results of screening program

Ethnic group	*n*	*%*	*Abnormal glucose load test*	*Abnormal GTT*
Hispanic	1,943	46.2	16.2	4.2
Chinese	794	18.9	24.7	7.3
Black	521	12.4	9.2	1.7
Non-Hispanic white	322	7.7	14.9	1.6
Filipina	265	6.3	23.8	6.0
Other Asian	232	5.5	13.4	5.6
Pacific Islander	74	1.8	18.9	8.1
Middle Eastern	41	1.0	26.8	7.3
Native American	18	0.4	11.1	0.0
TOTAL	4210		17.3	4.5

Table II. Maternal characteristics of study population

Maternal characteristic	*Hispanic (n = 1745) (mean ± SD)*	*Chinese (n = 797) (mean ± SD)*	*Black (n = 509) (mean ± SD)*	*Non-Hispanic white (n = 315) (mean ± SD)*
Age at screen (yr)	25.6 ± 5.6	29.0 ± 4.5	23.7 ± 5.4	26.5 ± 6.2
Weight at screen (kg)	67.5 ± 11.3	58.3 ± 7.5	76.2 ± 16.3	72.3 ± 15.4
Height at screen (cm)	155.5 ± 5.9	145.1 ± 9.4	163.0 ± 8.4	163.6 ± 6.3
Body mass index	27.9 ± 4.2	24.0 ± 2.6	28.8 ± 5.5	27.0 ± 4.9
Obese (>120% IBW) (%)	40.0	7.0	41.0	34.0
Parity (%)				
0	47.1	61.8	55.7	59.9
1-2	41.0	33.9	35.3	35.1
3+	11.9	4.3	9.0	5.0

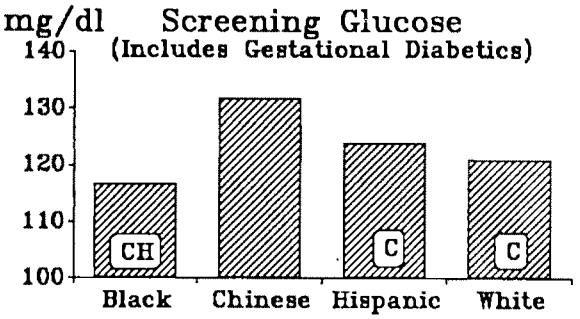
IBW, Ideal body weight.

mass index (kilograms per square meter) was calculated from height and weight at the time of screening. Maternal ethnicity, as self-identified, was recorded into more than 50 categories. These categories were combined into nine major groups for the purpose of this analysis. To simplify statistical analysis, we included only the first glucose load test for each individual that was performed between 26 and 32 weeks' gestation. Women with pregestational diabetes and those receiving β-adrenergic receptor agonist therapy for management of preterm labor or asthma were excluded. For women undergoing a GTT, the area under the glucose curve was calculated with a standard formula: Glucose area = (Fasting + 1 hour + 2 hour + 3 hour) − 0.5 (Fasting + 3 hour).

Data were analyzed with a general linear models approach to determine the roles of maternal age and body mass index in glucose tolerance. A two-way analysis of variance was used to examine interaction between ethnicity and the independent variables. Pairwise comparisons were made between the ethnic groups, and adjusted means were calculated for the dependent variables by setting the value of each covariate at its mean.

Results

Table I shows the ethnic variation in the incidence of abnormal results of glucose load tests and GTTs for the entire screened population. There was marked variation in the incidence of abnormal glucose load tests. A particularly high incidence was observed among Chinese and Filipino women. Pacific Islander and Middle Eastern women also had a high percentage of abnormal glucose load test results, although the number of women in these groups was too small to analyze. In contrast, a very low incidence of abnormality was seen in black women. Non-Hispanic white and Hispanic women had an intermediate incidence of abnormality. Although the numbers of Native Americans were quite small, it is interesting to note that the incidence of abnormal screening test results was low. The incidence of gestational diabetes mellitus among the ethnic groups followed a similar pattern in most respects. Chinese, Filipino, and Middle Eastern women had the highest incidence of gestational diabetes mellitus. Hispanic women were intermediate, while black and non-Hispanic white women had the lowest incidence. The latter group had the highest false-positive rate for glu-



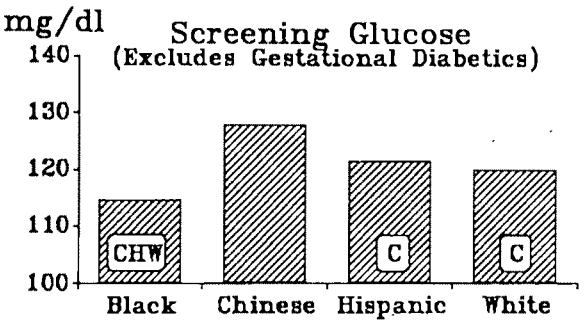
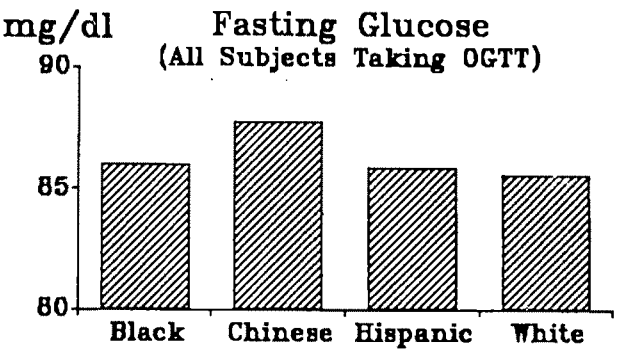


Fig. 1. Adjusted values of screening glucose by ethnic group. *Top,* Includes women with gestational diabetes; *bottom,* excludes women with gestational diabetes ($p < 0.05$).



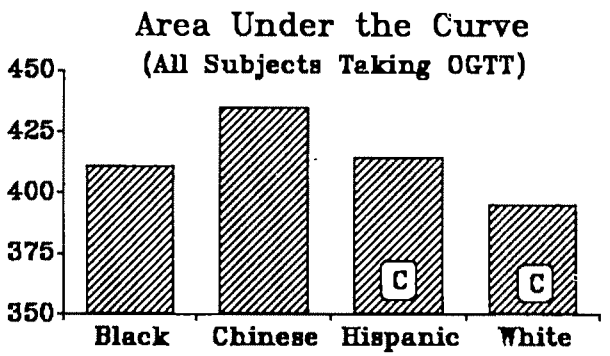


Fig. 2. Results for all subjects undergoing oral GTT by ethnic group. *Top,* Fasting values of glucose; *bottom,* area under the curve ($p < 0.05$).

cose load test results when judged by the results of the GTT. No cases of gestational diabetes mellitus were identified among the small numbers of Native American women in our population.

The subsequent analysis was limited to the four largest ethnic groups: Chinese, Hispanic, black, and non-Hispanic white. Chinese and Hispanic subjects were grouped on the basis of language. The "Chinese" sample is relatively homogeneous, deriving from the Han populations in southern China, as well as Chinese-speaking individuals from mainland China, Taiwan, and Hong Kong. The "Hispanic" sample comprises Spanish-speaking individuals from Mexico and various Central and South American countries. The degree of admixture with black and non-Hispanic white is not known.

Table II shows demographic variables for these four groups. Values are noted as significantly different at $p < 0.05$. Chinese women were significantly older than women in the remaining three groups, while black women were significantly younger. Non-Hispanic white and Hispanic women were close in age, but the difference was still significant.

Body size and proportionality differed significantly between the four groups. Chinese mothers were significantly lighter in weight than black, Hispanic, and non-Hispanic white mothers, and Hispanic women were significantly lighter than both black and non-Hispanic white women. Chinese and Hispanic women were significantly shorter than black and non-Hispanic white mothers. Chinese women had a significantly lower body mass index than the other three groups. Non-Hispanic white women had a significantly lower body mass index than either black or Hispanic women. Chinese and non-Hispanic white mothers had significantly lower parity than either black or Hispanic mothers. The black and Hispanic samples had the highest number of obese women; the Chinese sample had the lowest number of obese women.

Table III details the results of the screening program for the four major ethnic groups. Fig. 1 illustrates the comparisons of the adjusted means for each ethnic group. Where adjusted mean values differ, the letter of the ethnic group (*C* for Chinese, *B* for black, *W* for non-Hispanic white, and *H* for Hispanic) whose adjusted mean value is significantly larger ($p < 0.05$) is shown in the column for the ethnic group with the smaller value. Chinese women had a higher screening

Table III. Results of screening program

	Hispanic	*Chinese*	*Black*	*Non-Hispanic white*
Glucose load test				
Screening glucose (mean ± SEM)	124.4 ± 0.9*	134.8 ± 1.2	113.3 ± 1.3	121.4 ± 1.6
Glucose, adjusted (mean ± SEM)	124.0 ± 0.8	131.9 ± 1.4	116.9 ± 1.6	121.1 ± 2.0
Abnormal glucose load test (>140 mg/dl) (%)	17	25	9	14
All GTTs				
n	299	205	44	40
Results (No.)				
Abnormal	71 (33%)	56 (27%)	9 (29%)	4 (10%)
Borderline	51 (17%)	36 (17%)	7 (15%)	5 (12%)
Normal	177 (59%)	113 (55%)	28 (63%)	31 (77%)
Glucose area	418.5 (4.2%)	434.9 (5.4%)	418.0 (15.9%)	394.2 (9.9%)
Glucose area; adjusted	414.7 (4.7%)	435.4 (5.8%)	411.3 (11.8%)	395.3 (12.4%)
Abnormal GTTs				
Glucose area, adjusted (mean ± SEM)	518.8 ± 8.4	516.2 ± 10.2	585.1 ± 23.8	510.2 ± 35.9
Fasting glucose, adjusted (mean ± SEM)	95.0 ± 1.6	93.4 ± 1.5	97.5 ± 4.6	86.6 ± 6.9
Fasting glucose (>105 mg/dl) (n)	19 (25.7%)	8 (24.3%)	5 (55.6%)	0 (0%)

*Adjusted for maternal age and body mass index.

serum glucose level than any other group ($p < 0.0001$). Black women had a significantly lower screening serum glucose value than Chinese or Hispanic women ($p < 0.0001$). The screening serum glucose values for non-Hispanic white and Hispanic women were not significantly different. After adjustment for maternal age and body mass index, the mean screening blood glucose level for Chinese women still remained significantly higher than that for the other three ethnic groups ($p < 0.0001$), and that for black women remained significantly lower than that for Hispanic and Chinese women ($p < 0.0001$). To examine whether this result was due to a larger number of cases of gestational diabetes in the Chinese sample or to a real difference in screening glucose values between the ethnic groups, we repeated the analysis for calculating adjusted means excluding women with gestational diabetes (two or more abnormal values on GTT) from all the ethnic groups. As Fig. 1 illustrates, when cases of gestational diabetes were removed from the sample, black women had significantly lower screening glucose values than Chinese, Hispanic, and non-Hispanic white women ($p < 0.0001$). Hispanic and non-Hispanic white women had significantly lower screening glucose values than Chinese women ($p < 0.0001$) when women with gestational diabetes were removed from the analysis.

A total of 588 women in these four groups underwent a GTT (Table III). The proportion of abnormal GTT results was significantly higher in Hispanic and Chinese women than in black and non-Hispanic white women. Non-Hispanic white women had a lower proportion of abnormal test results than any of the three remaining groups. Chinese women had significantly higher total areas under the curve ($p < 0.05$) (Fig. 2). When the area under the curve was adjusted for age and body mass index (Table III), Chinese women still had a significantly higher total glucose area than either Hispanic or non-Hispanic white women. In those women who had an abnormal GTT result (Table III), there were no significant differences in the total area under the glucose curve between the ethnic groups. Black women had significantly higher unadjusted fasting glucose values (Table III) than any of the remaining groups, as well as a higher proportion of fasting glucose levels >105 mg/dl. In contrast, Chinese women had significantly lower values for unadjusted fasting glucose and a significantly lower proportion of results over the threshold for abnormality. The results for Hispanic and non-Hispanic white women were similar (Table III). Fig. 2 illustrates adjusted fasting glucose values for women having a GTT. Chinese women had the highest values, while black, Hispanic, and non-Hispanic white women had similar values. None of these values were significant.

Comment

This study demonstrates differences in glucose tolerance in pregnancy between four ethnic groups studied. Since maternal variables of age and body habitus were controlled for in the analyses, ethnic differences

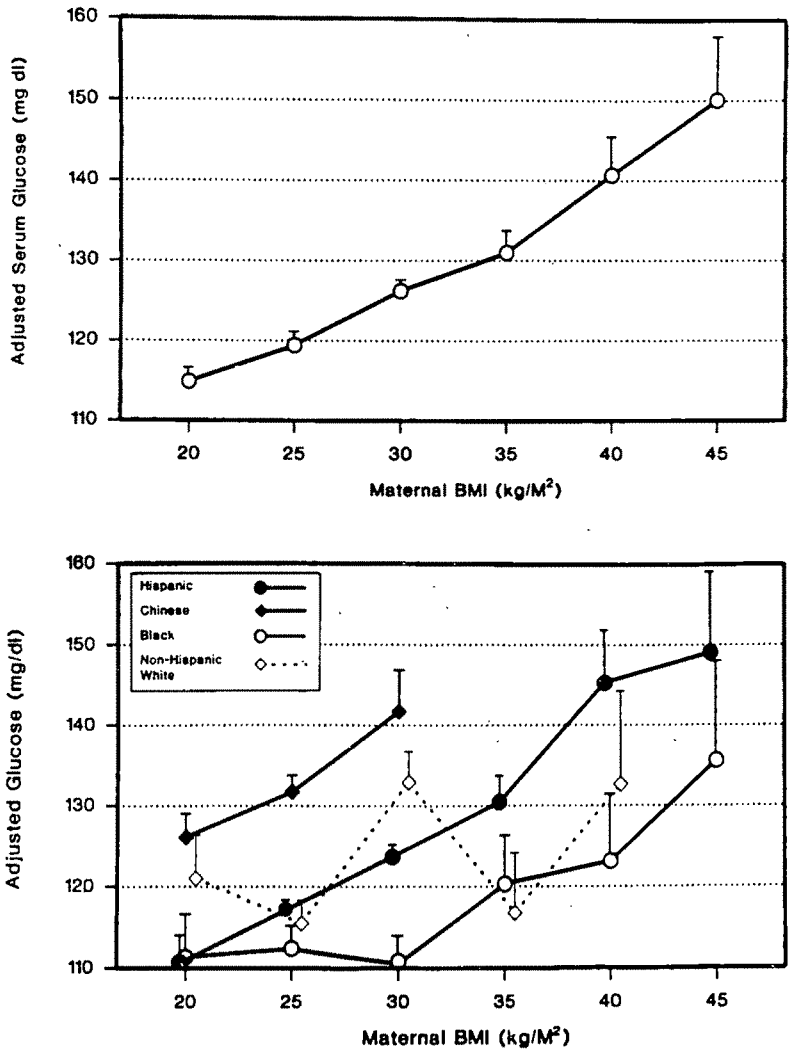


Fig. 3. *Top,* Adjusted screening glucose level by maternal body mass index, all ethnic groups combined. For each body mass index stratum the data point represents the least-square mean (+1 SEM) derived from an analysis of covariance with age and ethnic group controlled. *Bottom,* Adjusted screening glucose by maternal body mass index group in Hispanic, Chinese, black, and non-Hispanic white women. For each body mass index stratum the data point represents the least-square mean (+1 SEM) derived from an analysis of covariance with age and ethnic group controlled.

were not explained by these factors. In a separate regression analysis performed for each ethnic group individually, age and body habitus were significantly associated with deterioration of glucose tolerance, particularly for Chinese women. Evidence of worsening glucose tolerance with advancing age was found in all four ethnic groups, with a trend toward more age-related deterioration in black than in non-Hispanic white women. These findings are consistent with previous reports[8, 11, 12] and support the concept that many women with gestational diabetes have the potential for the development of diabetes after delivery.

The screening glucose levels of Chinese women were substantially higher than those of other ethnic groups when matched for body mass index. Chinese women had significantly higher screening glucose values even when women with gestational diabetes were removed from the analysis. These data support the hypothesis that results from the screening test results are clearly different between the ethnic groups and that these differences are not due to a higher frequency of gestational diabetes among the Chinese.

Obesity is an acknowledged risk factor for the development of both gestational diabetes mellitus and diabetes in later life.[8, 11] In the present study all four ethnic groups showed some evidence of worsening glucose tolerance with increasing body mass index, but the response was not entirely uniform. Chinese and Hispanic

women exhibited more marked deterioration (Fig. 3) in glucose tolerance with increasing body mass index than did black women until a state of moderate obesity was reached. It is possible that glucose intolerance in black women is relatively immune to the effect of mild to moderate obesity. In contrast, there was marked deterioration of glucose tolerance in both the Hispanic and Chinese groups with even mild obesity. We do not know if the pattern of obesity, even mild obesity, is important in the risk of diabetes mellitus among gravid women. This question deserves further investigation in light of recent studies linking fat patterns with diabetes mellitus in adults.[15]

This study does not address directly the issue of standards for the oral GTT in pregnancy. The definition of abnormality for the National Diabetes Data Group criteria was based on 95% confidence limits of unselected oral glucose load test results in non-Hispanic white and black women.[6] On the basis of a comparison of Israeli and U.S. populations, Friedman et al.[16] argue that the standards for abnormality should be adjusted for both ethnic and age factors. In effect, this approach would maintain the incidence of gestational diabetes mellitus constant across dissimilar groups. Such an approach presumes that the fetus responds relative to some ethnic and/or constitutional "norm" rather than according to an absolute threshold of glucose abnormality. There is no direct evidence to support this concept. Therefore, despite our finding of significant ethnic differences, the validity or necessity of constructing "ethnicity-specific" test thresholds remains to be demonstrated.

The threshold of glycemia for diabetic fetopathy in late pregnancy is not known and may not be constant for all morbidities. Moreover, if such a threshold exists, it may be substantially modified by other factors, including the coexistence of obesity. It has been argued that the National Diabetes Data Group standards are too "liberal" and that morbidity is better predicted by the WHO criteria.[14] Conversely, it has been argued that even women with a single abnormal value on a 3-hour GTT have evidence of increased neonatal morbidity.[17, 18] In the study by Langer et al.,[17] black and white women with a single abnormal value on oral GTT were compared with matched control subjects who had either gestational diabetes mellitus or normal oral GTT results. The incidence of neonatal abnormalities (particularly the incidence of macrosomic infants and the metabolic abnormalities including polycythemia) was significantly increased with one abnormal value. It is unclear if glucose tolerance has an impact on the pattern of fetal growth and whether maternal obesity and ethnicity are important covariables. Until such relationships are better understood, arguments about the threshold for abnormal glucose tolerance in late pregnancy will remain largely moot.

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Gestational diabetes mellitus: The prevalence of glucose intolerance and diabetes mellitus in the first two months post partum

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To determine the prevalence of abnormal carbohydrate metabolism in the early postpartum period in women with gestational diabetes mellitus, we performed 2-hour oral glucose tolerance tests between 5 and 8 weeks post partum in 246 women with recent gestational diabetes mellitus. Patients were stratified into three study groups based on their fasting serum glucose level during pregnancy: (1) group A_1: all fasting serum glucose levels during pregnancy <105 mg/dl without insulin therapy; (2) group A_2: any fasting serum glucose levels >105 and <140 mg/dl before insulin therapy; (3) group B_1: any pregnancy with fasting serum glucose levels >140 mg/dl. Overall, 48 (19%) of the patients had an abnormal oral glucose tolerance test in the early postpartum period; 25 (10%) had impaired glucose tolerance and 23 (9%) had diabetes mellitus. The prevalence of postpartum diabetes mellitus (2% in group A_1, 9% in group A_2 and 44% in group B_1) increased in parallel with the degree of maternal metabolic decompensation during pregnancy ($p < 0.05$ for A_1 versus A_2; $p < 0.001$ for A_2 versus B_1). The prevalence of impaired glucose tolerance was likewise greater in the B_1 group (26%) than in either the A_1 or the A_2 group ($p < 0.05$). Gestational age <24 weeks at diagnosis of gestational diabetes mellitus was an additional risk factor for postpartum glucose intolerance. Our findings support the use of an oral glucose tolerance test in the early puerperium, especially for patients with elevated fasting serum glucose levels during pregnancy. (Am J Obstet Gynecol 1990;163:93-8.)

Key words: Gestational diabetes, glucose tolerance, non-insulin-dependent diabetes

Gestational diabetes mellitus is currently defined as "carbohydrate intolerance of variable severity with onset of first recognition during the present pregnancy."[1, 2] This definition does not restrict the severity of carbohydrate intolerance, nor does it exclude possible pregestational or postpartum glucose intolerance. Indeed, existing data suggest that women with gestational diabetes may have had undiagnosed glucose intolerance before pregnancy[3] and frequently have abnormal glucose tolerance within the first year post partum.[4-6] These patients also have an increased risk of overt diabetes later in life.[7-13] The appropriate time to begin detection of glucose tolerance abnormalities in women with prior gestational diabetes mellitus has not been defined. Because most patients have a routine postpartum examination approximately 5 to 8 weeks after delivery, we reasoned that this might be a useful time to test patients for glucose intolerance. Therefore we performed this study to determine the prevalence of abnormal carbohydrate tolerance between 5 and 8 weeks post partum in women with recent gestational diabetes mellitus. Furthermore, we attempted to relate the prevalence to the severity of metabolic decompensation during pregnancy, as indexed by fasting serum glucose levels. Finally, we examined maternal age, body mass index, and gestational age at the time of diagnosis as possible predictors of abnormal postpartum glucose tolerance.

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Material and methods

Subjects. During 1987, the period of this study, 16,363 women were delivered of their infants at Los Angeles County–University of Southern California Women's Hospital. Most were referred from 16 local prenatal care clinics. In accordance with the Second International Workshop-Conference on gestational diabetes mellitus,[2] prenatal clinic patients undergo a serum glucose determination 1 hour after a 50 gm oral glucose load between 24 and 28 weeks of gestation, or on entry if prenatal care commenced after 28 weeks. Women who are seen before 24 week with one or more risk factors for gestational diabetes mellitus (history of macrosomia, prior gestational diabetes mellitus, prior stillbirth, glycosuria, maternal obesity, hypertension,

Table I. Mean age and postpartum body mass index of women with gestational diabetes mellitus stratified according to antepartum fasting glucose levels*

Study group	*Age (yr)*	*Body mass index (kg/m²)*
A_1 (n = 100)	30 ± 1	29 ± 1
A_2 (n = 123)	30 ± 1	30 ± 1
B_1 (n = 23)	30 ± 1	32 ± 1

BMI, Body mass index.

*A_1, A_2, and B_1 denote women with antepartum fasting serum glucose levels <105, 105 to 139, and >139 mg/dl, respectively. Numbers in parentheses denote the number of women in each group. Body mass index denotes body weight/(height)². None of the differences between group mean values was statistically significant.

family history of diabetes, or maternal age >35 years) were screened at their initial visit and again at 24 to 28 weeks' gestation. Patients with a 1-hour glucose screen ≥140 mg/dl underwent a 3-hour, 100 gram oral glucose tolerance test (GTT) in accordance with national Diabetes Data Group guidelines.[1] Women with gestational diabetes mellitus had weekly fasting serum glucose determinations; postprandial serum glucose levels were not measured. Women whose fasting serum glucose levels were consistently <105 mg/dl were managed with diet therapy alone. Those who had two fasting serum glucose values ≥105 mg/l, or those with any fasting serum glucose level ≥140 mg/dl were treated with diet and insulin. Insulin therapy was not required in any patients during the puerperium. Subjects for this study were recruited at the time of delivery at Women's Hospital. The study was approved by the Research Committee of the Los Angeles County–University of Southern California Medical Center.

Postpartum testing. After 3 days of a diet that provided at least 150 gm/day of carbohydrate, patients fasted overnight (10 to 16 hours), then ingested 75 gm of glucose over 5 minutes. Serum specimens were obtained by repeated venipuncture at −5, +30, +60, +90, and +120 minutes. Specimens were transported on ice for immediate separation of serum and cells. Serum was stored at −20° C for subsequent glucose measurement (Glucose Analyzer II, Beckman Instruments, Fullerton, Calif.). Postpartum glucose tolerance results were interpreted according to National Diabetes Data Group criteria.[1] Some women had postpartum oral GTT results that fit neither the normal nor the impaired category in the National Diabetes Data Group classification. We included these subjects in the normal category for the purposes of data analysis because they did not have sufficient hyperglycemia to warrant classification as impaired glucose tolerance.

Data analysis

Subject classification. Patients were stratified by their degree of metabolic decompensation during pregnancy, as indexed by the initial fasting serum glucose of their antepartum oral GTT and by their fasting serum glucose levels before insulin therapy. Three study groups were defined: group A_1: all patients with fasting serum glucose levels <105 mg/dl without insulin therapy, group A_2: any patient with a fasting serum glucose ≥105 mg/dl and <140 mg/dl before any insulin therapy, and group B_1: any patient whose fasting serum glucose was ≥140 mg/dl (Table I).

Statistical analysis. Data are presented as mean ± SE. The statistical significance of differences among the three study groups with respect to categoric variables (i.e., postpartum glucose tolerance status, antepartum study classification, and gestational age at diagnosis ≤24 or >24 weeks) was determined with χ^2 or Fisher's exact test. Statistical significance was assessed after adjusting for multiple comparisons when appropriate. The relationship between continuous variables (age, body mass index, or pregnancy fasting serum glucose) and postpartum glucose tolerance status was assessed by analysis of variance or, if the data were not normally distributed, by the Kruskal-Wallis test. When these tests revealed significant difference in distribution of means among groups, the Tukey's multiple comparison procedure was used to identify intergroup differences.

Results

Patient classification. In 1987, 525 women with the diagnosis of gestational diabetes mellitus were interviewed in the immediate postpartum period and scheduled for follow-up evaluation of carbohydrate tolerance between 5 and 8 weeks post partum. Of these, 274 women kept their follow-up appointments, and underwent a postpartum oral GTT between 5 and 8 weeks after delivery. Twenty-eight of these patients were excluded from analysis because their antepartum oral GTT results were incompletely documented. Thus 246 patients were included in the final analysis. Ninety-eight percent of these patients had Spanish surnames.

Of the 246 study patients, 100 (41%) were classified as belonging to group A_1, 123 (50%) as A_2, and 23 (9%) as B_1 (Table I). The distribution of classes among the 251 women who did not return for a postpartum oral GTT was similar: 35% in group A_1, 51% in A_2, and 14% in B_1 ($p > 0.2$ compared with the 246 study patients).

Body mass index (kg/m²) was determined at the time of the postpartum oral GTT. Overall, 74% of the patients were obese (body mass index ≥27). Each of the three study groups had a mean body mass index indicative of obesity (Table I). There were no significant

differences in body mass index among the groups. Likewise, mean age did not differ significantly among groups (Table I).

Postpartum glucose tolerance. Overall, 81% of patients had normal or unclassifiable oral GTT results between 5 and 8 weeks post partum. An additional 10% had impaired glucose tolerance and the remaining 9% had diabetes mellitus. The proportions of women with normal, impaired, and diabetic oral GTTs in each of the three antepartum groups appear in Table II. The majority (90%) of the 100 women in the A_1 group had normal postpartum glucose tolerance. Only 8% of these women had impaired glucose tolerance and an additional 2% had diabetes mellitus. Of the 123 women in the A_2 group, 101 (82%) had normal early postpartum carbohydrate tolerance. Half of the remaining 22 women (9% overall) had impaired glucose tolerance, similar to the 8% prevalence of impaired glucose tolerance in the A_1 group. However, an additional 9% of the A_2 group had diabetes mellitus in the puerperium, a prevalence that was significantly greater than that of the A_1 group ($p < 0.03$).

Both diabetes mellitus and impaired glucose tolerance were common in the B_1 group post partum. Of the 23 women in that group, only seven (30%) had normal glucose tolerance in the early puerperium. Six (26%) had impaired glucose tolerance, and 10 (44%) had diabetes mellitus. Statistical analysis revealed that the prevalence of diabetes mellitus ($p < 0.01$) and of impaired glucose tolerance ($p < 0.05$) post partum was each greater in the B_1 than in either the A_1 or the A_2 group. Thus marked fasting hyperglycemia during pregnancy (class B_1) was associated with an increased risk of both diabetes mellitus and impaired glucose tolerance in the puerperium. Less severe fasting hyperglycemia during pregnancy (class A_2) was also associated with an increased risk of diabetes mellitus but not with impaired glucose tolerance compared with women without fasting hyperglycemia during pregnancy.

The gestational age at time of diagnosis of gestational diabetes mellitus was examined as another possible predictor of abnormalities in postpartum glucose tolerance. As expected from the design of our antepartum screening program for gestational diabetes mellitus, the majority (203/246 or 82%) of cases were diagnosed during or after the twenty-fourth week of gestation (Table III). Only 43 (18%) were diagnosed before this time. However, those women diagnosed before 24 weeks had a significantly greater prevalence of abnormal oral GTTs in the early puerperium than did women diagnosed after 24 weeks (44 versus 14%; $p < 0.001$).

To determine whether elevated antepartum fasting serum glucose levels and an early gestational age at diagnosis imparted independent risks of abnormal glucose tolerance postpartum, we used multivariate analysis to compare the distributions of antepartum fasting serum glucose levels and of gestational age at diagnosis among the three postpartum glucose tolerance categories (Table IV). After adjustment for the effects of gestational age at diagnosis, antepartum fasting serum glucose levels in women with normal and impaired glucose tolerance post partum were slightly, but not significantly, different (101 ± 2 and 113 ± 5 mg/dl, respectively). The antepartum fasting serum glucose levels in women with postpartum diabetes mellitus (144 ± 5 mg/dl) were significantly higher than in the normal and impaired glucose tolerance groups ($p < 10^5$). Similarly, after adjustment for the effects of fasting serum glucose, gestational ages at diagnosis of gestational diabetes mellitus in women with postpartum impaired glucose tolerance and diabetes mellitus were not different (25 ± 1 and 24 ± 1 weeks, respectively) but were significantly less than in women with normal glucose tolerance post partum (30 ± 1 weeks; $p < 0.003$). Thus we found elevated FSG levels and an early gestational age at the diagnosis of gestational dibetes mellitus to be independent risk factors for abnormal glucose tolerance in the puerperium.

We found no significant differences in mean age (30 ± 1, 30 ± 1, and 29 ± 1 years, respectively) or body mass index (30 ± 1, 31 ± 1, and 31 ± 2 kg/m,^{2} respectively) among groups with normal, impaired, and diabetic glucose tolerance post partum.

Fasting serum glucose in the detection of postpartum diabetes. The diagnosis of diabetes in nonpreg-

Table II. Prevalence of normal, impaired, and diabetic glucose tolerance test results in women with recent gestational diabetes mellitus*

Study group	*Normal*	*IGT*	*NIDDM*
A_1	90	8	2
(n = 100)	(90%)	(8%)	(2%)
A_2	101	11	11
(n = 123)	(82%)	(9%)	(9%)†
B_1	7	6	10
(n = 23)	(30%)	(26%)†,‡	(44%)†,‡

IGT, Impaired glucose tolerance; *NIDDM*, non-insulin-dependent diabetes mellitus.

*Study groups are defined in Table I. Numbers in parentheses denote the number of women in each group. Glucose tolerance tests were performed 6 to 8 weeks post partum and interpreted according to National Diabetes Data Group criteria. The statistical significance of intergroup differences in the prevalence of each postpartum diagnosis is denoted.

†$p < 0.05$ versus A_1.

‡$p < 0.05$ versus A_2.

Table III. Prevalence of normal, impaired, and diabetic glucose tolerance in nonpregnant women with recent gestational diabetes mellitus diagnosed before or after 24 weeks' gestation*

Gestational age at diagnosis	*Normal*	*IGT*	*NIDDM*
<24 wk (n = 43)	24 (56%)	10* (23%)	9* (21%)
≥24 wk (n = 203)	174 (86%)	15 (7%)	14 (7%)

See Table II for abbreviations. *Normal, IGT,* and *NIDDM* denote postpartum glucose tolerance test results according to National Diabetes Data Group criteria. Numbers in parentheses denote the number of subjects diagnosed before or at/after 24 weeks' gestation. Numbers in parentheses denote the prevalence (percent) of each diagnosis in those groups. The statistical significance of differences in the prevalence of diagnoses between groups is denoted.

*$p < 0.05$.

Table IV. Antepartum fasting serum glucose levels and gestational ages at diagnosis of gestational diabetes mellitus in women with normal, impaired, and diabetic glucose tolerance tests post partum*

	Normal	*IGT*	*NIDDM*
Antepartum FSG (mg/dl)	101 ± 2	113 ± 5	144† ± 5
Gestational age at diagnosis of gestational diabetes mellitus (wk)	30‡ ± 1	25 ± 1	24 ± 1

FSG, Fasting serum glucose level; *IGT,* impaired glucose tolerance; *NIDDM,* non-insulin-dependent diabetes mellitus.

**Antepartum FSG* denotes the initial fasting serum glucose level obtained during the antepartum oral GTT or, in the case of patients first seen with a fasting serum glucose level ≥ 140 mg/dl, the initial fasting serum glucose level obtained. The statistical significance of differences in the prevalence of diagnoses between groups is denoted.

†$p < 0.001$ versus normal and impaired glucose tolerance.

‡$p < 0.01$ versus impaired glucose tolerance and non-insulin-dependent diabetes mellitus.

nant adults can be based on fasting serum glucose levels ≥140 mg/dl, a sufficiently abnormal oral GTT, or both.[1] With the fasting serum glucose levels obtained at the time of postpartum oral GTTs, we examined the utility of a fasting serum glucose level ≥140 mg/dl in detecting diabetes in our nonpregnant patients. Of the 23 women who met diagnostic criteria for non-insulin dependent diabetes mellitus postpartum, only seven (30%) had a fasting serum glucose level ≥140 mg/dl at the time of their postpartum oral GTT. The remaining sixteen women (70% overall) would have escaped detection by screening for a fasting serum glucose level ≥140 mg/dl in the early puerperium. We further analyzed our data to determine whether there was a level of fasting glycemia in the puerperium below which the diagnosis of early postpartum diabetes mellitus was unlikely. We found that 20 of the 23 women with postpartum diabetes mellitus had fasting glucose levels >115 mg/dl. However, the remaining three women with postpartum diabetes mellitus had fasting serum glucose levels <105 mg/dl.

Comment

The primary objective of this study was to determine whether routine glucose tolerance testing at 5 to 8 weeks post partum in women with recent gestational diabetes mellitus would detect an important number of women with abnormal glucose tolerance after pregnancy. We also sought to identify maternal characteristics that would place women at particularly high risk for diabetes in the puerperium. Therefore at the time of delivery we recommended early postpartum glucose tolerance testing to 525 women with gestational diabetes mellitus. Approximately half the women returned for the recommended testing. The fact that we could identify no differences in the distribution of gestational diabetes mellitus cass (A_1, A_2, and B_1) between the women who did and those who did not return for testing suggests that those who did return were not self-selected for any particular risk of diabetes of impaired glucose tolerance post partum. Of the 243 women who did return for early postpartum testing, approximately one in five had an abnormal oral GTT result; half of these met current diagnostic criteria for non-insulin-dependent diabetes mellitus. Thus glucose tolerance was clearly abnormal in many of our patients soon after delivery. This finding supports the proposition of Harris[3] that abnormal glucose tolerance may actually antedate pregnancy in some women with gestational diabetes mellitus. As detailed by Metzger et al.,[6] this may be particularly true for women with marked hyperglycemia during pregnancy.

Because most of our patients had normal glucose tolerance at 5 to 8 weeks post partum, we examined several factors that we thought would identify the high-risk women most appropriate for early postpartum glucose tolerance testing. We found that an elevated maternal fasting serum glucose level during pregnancy and an early gestational age at diagnosis of gestational diabetes mellitus were associated with an increased risk of diabetes mellitus and impaired glucose tolerance in the puerperium. With regard to fasting serum glucose data, nearly 10% of women with fasting glucose levels of 105 to 139 mg/dl during pregnancy had diabetes within 5 to 8 weeks of delivery; 44% of our patients with fasting serum glucose levels ≥140 mg/dl during gestation had diabetes in the puerperium. These fast-

ing serum glucose results are consistent with the pattern reported by Metzger et al.[6] within 1 year after delivery and seem to indicate that the metabolic derangement(s) that lead to fasting hyperglycemia during pregnancy are not specific for gestation. Rather, it appears that an elevated fasting serum glucose level during pregnancy is a marker for underlying metabolic abnormalities that may have preceded pregnancy,[3] which are clearly present in some women very soon after delivery, and that predict a high likelihood of diabetes in later life.[8]

The threefold increase in the prevalence of postpartum oral GTT abnormalities in women diagnosed with gestational diabetes mellitus before 24 weeks' gestation may have been a function of the protocol currently used to detect gestational diabetes. Women were tested before 24 weeks only if they had risk factors for gestational diabetes mellitus. Some of these risk factors (e.g., obesity and a family history of diabetes) are also risk factors for nonpregnant diabetes. The women diagnosed before 24 weeks' gestation were thus a select minority of patients with known risk factors for diabetes outside of pregnancy. This may explain their increased risk of postpartum glucose tolerance abnormalities. We found neither maternal age nor postpartum body mass index to be useful predictors of abnormal glucose tolerance in the puerperium, perhaps because our patients were rather homogeneous with regard to these two variables.

The prevalence of glucose tolerance test abnormalities in our patients with recent gestational diabetes mellitus is lower than that reported by Metzger et al.[6] within 4 to 12 months after delivery. Several factors may have contributed to this difference. First, we used a smaller glucose challenge (75 gm) than did those authors (100 gm). Probably more important is the earlier time after delivery at which we studied our patients. Clinical experience indicates that insulin requirements fall very quickly after delivery. The fact that many women with pregestational diabetes require little or no insulin in the early puerperium suggests that insulin action may actually be better postpartum than it was before conception. The time course of return to a prepregnancy equilibrium in carbohydrate metabolism, if this in fact occurs, is unknown. Therefore it is possible that we examined women at a time when their glucose tolerance was optimized. Our continued follow-up should reveal whether the incidence of diabetes and impaired glucose tolerance in our Hispanic patients at 6 to 12 months post partum truly differs from that reported by Metzger et al.

What is the relevance of our findings to clinicians caring for women with gestational diabetes mellitus? First, we suggest that women with fasting serum glucose levels $\geq$140 mg/dl during pregnancy should have an oral GTT at their initial postpartum visit because we found that 44% of these women had diabetes at that time. Second, in view of the 9% prevalence of diabetes mellitus and the additional 9% prevalence of impaired glucose tolerance in women with less marked fasting hyperglycemia (105 to 139 mg/dl) during pregnancy, we suggest that these women be tested at 5 to 8 weeks post partum. Finally, the 2% prevalence of diabetes mellitus and 8% prevalence of impaired glucose tolerance in the women with recent A_1 gestational diabetes mellitus suggest that routine glucose tolerance testing also be done in this group. Although most women in this last group will have normal oral GTTs soon after pregnancy, initiating a program of testing in the puerperium stresses the importance of periodic (e.g., annual) glucose tolerance testing at a time when their attention is focused on diabetes. Detection of diabetes in women who have the disease will allow the initiation of treatment with diet, medications, or both at a time when clinically apparent microvascular and neuropathic complications generally do not exist. Furthermore, documentation of abnormal carbohydrate tolerance aids in family planning recommendations.

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Indomethacin treatment for polyhydramnios and subsequent infantile nephrogenic diabetes insipidus

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A case of polyhydramnios was effectively treated with amniotic fluid decompression and indomethacin. Six months later nephrogenic diabetes insipidus was diagnosed and indomethacin was again effectively used. By reducing urine output, indomethacin controlled both in utero and extrauterine polyuria in this patient. (AM J OBSTET GYNECOL 1990;163:98-9.)

Key words: Polyhydramnios, indomethacin, diabetes insipidus

In a case reported by Kirshon and Cotton,[1] polyhydramnios was documented in a fetus with an extra unidentified marker chromosome. By reducing fetal urine output, indomethacin was successfully used to prevent reaccumulation of amniotic fluid after therapeutic amniocentesis. A clinical association was established between a chromosomal abnormality, an extra marker chromosome, and polyhydramnios. However, the exact cause of the polyhydramnios remained unknown until 6 months after delivery. The infant was discovered to have nephrogenic diabetes insipidus. We report here a retrospective analysis of polyhydramnios caused by nephrogenic diabetes insipidus and its overall management.

Case report

A 33-year-old gravida 3 now para 3-0-0-3 physician with no previous medical problems was hospitalized for abdominal distention and pain at 26 weeks' gestation. Her prenatal evaluation was normal except for a maternal serum α-fetoprotein level <0.4 of the median at 16 weeks' gestation. On admission a level II ultrasonographic examination showed a singleton, structurally normal fetus with polyhydramnios. Amniocentesis was performed for both chromosomal analysis and therapeutic decompression. Cytogenetic studies showed a 47,XX+ marker chromosome pattern in all 20 cells examined. The extra marker chromosome was a small ring chromosome of unknown origin. Peripheral blood studies performed after birth confirmed the presence of the ring chromosome in 70% of cells, whereas 30% showed a normal 46,XX chromosome pattern.

After removal of 3000 ml of amniotic fluid, indomethacin was initiated at 25 mg orally every 4 hours to control both preterm labor and to prevent reaccumulation of polyhydramnios. A marked diminution of fetal urine output was observed by serial ultrasonographic evaluations. Fetal echocardiography failed to show constriction of the ductus arteriosus. Indomethacin therapy was continued until 35 weeks' gestation. One week later spontaneous labor ensued, and a 2280 gm female infant with Apgar scores of 9 at 1 and 5 minutes was vaginally delivered. There were no apparent physical abnormalities of the neonate.

The infant was subsequently noted to be a poor feeder and consequently was admitted to the hospital at 6 months of age for failure to thrive. Significant physical findings included a dehydrated and irritable infant with a temperature of 101° F. Pertinent laboratory data included serum osmolality 305 mosm/L, urine osmolality 98 mosm/L, urine specific gravity 1.003, serum sodium 150 mEq/l, and urine sodium 13 mEq/L, confirming the presence of diabetes insipidus. The serum blood urea nitrogen and creatinine concentrations were 20 mg/dl and 0.3 mg/dl, respectively.

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A vasopressin challenge test failed to show a change in urine or serum osmolality. Results of a renal ultrasonographic examination were essentially normal. On the basis of the above information, the diagnosis of nephrogenic diabetes insipidus was made. On the sixth hospital day, indomethacin therapy was started at 2 mg/kg per day, resulting in a decrease in serum osmolality from 305 to 290 mosm/L, a decrease in serum sodium from 150 to 135 mEq/L, a 50% decrease in urine output, and an increase in urine osmolality from 98 to 140 mEq/L. At discharge the infant was well hydrated and was gaining weight. Sixteen months later, the child remains on indomethacin therapy, and her renal function (as measured by serum creatinine concentration) has remained normal. The child has not shown any adverse effects of indomethacin treatment.

Comment

The diagnosis of congenital nephrogenic diabetes insipidus in the infant was evident by (1) a history of polyhydramnios as a result of fetal polyuria in utero, (2) no underlying disorders such as obstructive uropathy known to cause nephrogenic diabetes insipidus, and (3) a low urine osmolality unresponsive to vasopressin. Therefore a fetus with polyhydramnios should be carefully examined at birth for electrolyte imbalances, even when a clinical association such as a chromosomal abnormality has been established. Congenital nephrogenic diabetes insipidus should be considered as a possible cause of polyhydramnios.

Although the exact mechanism for the antidiuretic action of indomethacin is unknown, this case serves to show the efficacy of indomethacin both in reducing antenatal fetal urine output and in treating polyhydramnios as well as controlling infantile nephrogenic diabetes insipidus.[2]

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Risk factors for third-degree and fourth-degree perineal lacerations in forceps and vacuum deliveries

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Third- and fourth-degree perineal lacerations occur frequently during operative vaginal deliveries. To identify risk factors for lacerations, 2832 consecutive forceps and vacuum extraction deliveries were analyzed. Third- and fourth-degree lacerations occurred in 30% of deliveries. Multiple logistic regression was used to control for intercorrelation between potential risk factors. Factors associated with increased risk for third- and fourth-degree lacerations were midline episiotomy, nulliparity, second-stage arrest, occipitoposterior position, low or mid station, use of forceps instead of vacuum, use of local anesthesia, and Asian race. When these factors were controlled, there was no effect of birth weight, faculty versus resident operator, gestational age, abnormalities of first-stage labor, or several other factors. Prevention of perineal lacerations requires that the operator identify the patient at risk. Possible options for management of high-risk patients include use of mediolateral episiotomy or no episiotomy, use of vacuum extraction instead of forceps, and use of conduction anesthesia. (Am J Obstet Gynecol 1990;163:100-4.)

Key words: Perineal lacerations, forceps delivery, vacuum extraction delivery, episiotomy

Lacerations of the perineum are frequent complications of operative vaginal delivery and have substantial long-term morbidity. Lacerations that disrupt the anal sphincter capsule are associated with prolonged weakness of the sphincter muscle[1-5] and incontinence of flatus or stool in up to 40% of cases.[1-3] Dyspareunia and perineal pain may persist for years after third-degree lacerations[1, 2] and significant permanent disfigurement of the perineum often occurs.[1] Lacerations that violate the rectal mucosa carry added risks of infection, wound breakdown, and rectovaginal fistula. Many require secondary operative repair and cesarean section is often recommended for subsequent deliveries.[5]

A rational attempt to prevent lacerations must begin with a clear understanding of the factors that contribute to their occurrence. For spontaneous deliveries risk factors for perineal laceration include nulliparity,[6-9] midline episiotomy,[6, 8-11] macrosomia,[6, 9] delivery by residents,[6] delivery in lithotomy position,[12] and Asian race.[6] However, different factors may be relevant in operative deliveries. This article presents an analysis of factors associated with perineal lacerations in a large number of consecutive forceps and vacuum deliveries.

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Material and methods

Moffitt Hospital is a teaching hospital of the University of California San Francisco. Since 1975 the hospital has maintained an ongoing computer data base that contains over 200 items of obstetric data on every delivery. Immediately after each delivery, data are coded onto forms by the delivering physician. The forms are reviewed by a professional chart abstractor before entry into the computer. Several logic checks and internal validity checks are performed during data entry to ensure a high degree of accuracy for each item entered.

Included in this study were all patients who had forceps or vacuum extraction delivery, vertex presentation, singleton gestation, gestational age >35 weeks, and delivery from January 1975 through July 1988. The one case coded as "high forceps" was excluded. Cases of failed forceps or vacuum extraction resulting in cesarean delivery were excluded. The study inclusion criteria were met in 2832 cases.

Lacerations were coded separately from episiotomy and included both spontaneous lacerations and extensions of episiotomy. Standard definitions for third- and fourth-degree lacerations were used: third-degree lacerations are those that disrupt the anal sphincter capsule but not the rectal mucosa; fourth-degree lacerations are those that involve the mucosa. First- and second-degree perineal lacerations, cervical and vaginal lacerations, and minor degrees of vulvar and periurethral trauma were not considered in this study.

The data base was recently revised to reflect the current classification of high, mid, low, and outlet forceps proposed by the American College of Obstetricians and

Table I. Risk factors for third- or fourth-degree perineal lacerations: univariate analysis

Factor	*n*	*Perineal lacerations (%)*	*Relative risk*	*p*
Parity				<0.0001
0	2115	35.1	1	
1	505	16.4	0.47	
2	139	13.7	0.39	
3	51	11.8	0.33	
≥4	22	0.0	0.00	
Episiotomy				<0.0001
None	175	14.3	1	
Midline	1890	39.8	2.81	
Mediolateral	767	9.6	0.68	
Operator				<0.0001
Faculty	664	22.0	1	
Resident	2124	32.6	1.48	
Second-stage arrest				<0.0001
Absent	1927	27.3	1	
Present	904	36.0	1.33	
Station				<0.01
Outlet	1160	26.7	1	
Low	1493	32.5	1.22	
Mid	179	31.3	1.17	
Anesthesia				<0.02
Epidural	1876	28.1	1	
Saddle	144	26.4	0.94	
None	48	29.2	1.04	
General	31	32.3	1.15	
Local-pudendal	467	35.8	1.27	
Combination	266	35.3	1.26	
Instrument				<0.05
Forceps	2223	31.0	1	
Vacuum	609	26.4	0.85	
Position				<0.10
Anterior	2325	29.5	1	
Transverse	196	28.6	0.97	
Posterior	311	35.4	1.20	
Ethnic group				<0.10
White	1009	31.5	1	
Black	168	31.0	0.98	
Hispanic	158	27.8	0.88	
Chinese	208	36.5	1.16	
Filipino	141	42.6	1.35	
Japanese	30	33.3	1.06	
Other	265	35.5	1.13	

Gynecologists.[13] In more than 1000 cases, the material in the data base was inadequate to reclassify the pelvic level; the information was extracted by review of the original delivery notes and reentered into the data base.

Information was not available with regard to the type of forceps used (e.g., Simpson, Elliot). Although not coded in the data base, the Malmström vacuum cup was used in the majority of vacuum extractions. In rare cases when both forceps and vacuum were used, the instrument actually used to deliver the fetal head was coded. With regard to anesthesia, the coding in the data base did not allow distinction between local perineal infiltration and pudendal block.

An attending physician was typically present at delivery. Most deliveries were performed by a junior resident with the direct assistance of either a senior resident or attending physician. Some patients were treated in the faculty private practice and these were typically delivered of their infants by a faculty member. The data base contains three fields describing the levels and actual roles of the persons involved in delivery. For this study these fields were collapsed into a single code representing delivery by faculty or resident.

For the initial univariate analyses, several variables that might reasonably be associated with lacerations were explored. Statistical significance of relations was assessed by Yates-corrected χ^2 for categorical variables and by t test for continuous variables.

Multiple logistic regression was performed because of possible intercorrelations between the variables. All variables with significant ($p < 0.05$) or marginal ($p < 0.10$) univariate associations with perineal laceration were entered together in a main-effects model to determine the effect of each variable while simultaneously controlling for the effects of all the others. A logit model was fit to generate a maximum likelihood esti-

Table II. Logistic regression of risk factors for third- and fourth-degree perineal lacerations

Variable	*Adjusted odds ratio*	*95% Confidence interval*
Episiotomy		
Midline vs mediolateral/none	7.81	5.92-10.30
Parity		
Nulliparous vs parous	3.56	2.70-4.69
Instrument		
Forceps vs vacuum	1.90	1.48-2.45
Position		
Posterior vs anterior/transverse	1.60	1.15-2.22
Arrest of descent		
Present vs absent	1.56	1.22-1.99
Anesthesia		
Local/pudendal vs conduction	1.49	1.19-1.88
Station		
Low/mid vs outlet	1.32	1.02-1.71
Ethnic group		
Asian vs white/black/Hispanic	1.31	1.04-1.63
Operator		
Faculty vs resident	1.22	0.93-1.59

mate of the regression coefficient for each variable. Odds ratios and 95% confidence intervals were calculated from the coefficients and their standard errors. Variables with significant associations are those for which the confidence interval does not include an odds ratio of 1. The regression was performed with the PROBIT/MODEL = LOGIT procedure of SPSS-X.[14]

Results

Third-degree lacerations occurred in 555 deliveries (19.5%) and fourth-degree lacerations in 296 deliveries (10.5%), an overall laceration rate of 30.0%.

In the univariate exploration the factors shown in Table I were found to have an association with third- and fourth-degree laceration. The use of midline episiotomy was associated with nearly a threefold increase in risk for laceration. Nulliparous women had more than twice the risk of laceration compared with parous women. Other significant factors were delivery by a resident, presence of second-stage arrest, delivery from a low or mid station, use of local anesthesia, and use of forceps rather than vacuum extraction. There was a tendency for more lacerations in occipitoposterior deliveries and in women of Asian descent; however, these effects were of only marginal significance in the univariate analysis.

When patients who had lacerations were compared with those who did not, there was no difference in birth weight (3439 ± 462 vs 3423 ± 479 gm); gestational age (40.1 ± 1.5 vs 40.1 ± 1.6 weeks); the incidence of abnormalities of first-stage labor (prolonged latent phase, protraction, arrest, precipitous labor); the fraction of patients in whom labor was induced or augmented; the use of manual, forceps, or vacuum rotations; prenatal weight gain (15.6 ± 5.4 vs 15.3 ± 5.1 kg); the fraction of women who drank alcohol during pregnancy; the fraction who smoked or the number of cigarettes smoked per day. There were small differences in the length of the first stage of labor (687 ± 354 vs 652 ± 350 minutes; $p < 0.02$), in maternal age (26.6 ± 5.4 vs 27.1 ± 5.4 years; $p < 0.01$), and in prepregnancy weight (55.2 ± 10.1 vs 57.1 ± 10.7 kg; $p < 0.001$). However, these small differences were attributable to differences in parity between the groups and they were not considered further.

Before the multivariate analysis was performed all the variables in Table I were collapsed into dichotomous categories and coded as either present or absent. The ethnic category "other" was composed predominantly of Southeast Asians, Pacific Islanders, Indians, and Native Americans, thus these cases were coded as "Asian" together with Chinese, Filipino, and Japanese women. The anesthesia category "combination" was composed predominantly of combinations of local anesthesia with either epidural or saddle block, presumably because of inadequate conduction anesthesia. These cases were coded as "local" anesthesia. The few cases with no anesthesia or general anesthesia were excluded. Cases with missing values for any of the variables were excluded. After exclusions, 1978 cases were eligible for logistic regression analysis.

The results of the logistic regression analysis are summarized in Table II. With the exception of operator, all the factors considered in the model were associated with a statistically significant risk for perineal laceration. The adjusted odds ratio is a measure of the relative risk for laceration controlled simultaneously for the effects of the other factors. Clearly, midline episiotomy and nulliparity were the most important factors. The additional contributions of instrument, position, arrest of descent, anesthesia, station, and ethnic group were statistically significant but relatively small.

It was surprising that the status of the operator (faculty vs resident) did not have a significant bearing on the risk of laceration in the multivariate analysis. On examination of the covariances, it was found that the residents had a 50% higher incidence of perineal lacerations than the faculty because they had more patients in the high-risk Asian ethnic group (35% vs 22% of deliveries; $p < 0.001$) and because they used mediolateral episiotomy less often (25% vs 35% of deliveries; $p < 0.001$). When these factors were controlled, the laceration rates of residents and faculty were not significantly different.

Table III. Relationship between episiotomy and fourth-degree lacerations

Episiotomy	*No.*	*Fourth-degree lacerations*		*Relative risk*
		n	*%*	
Midline	1890	282	14.9	1
None	175	9	5.1	0.34*
Mediolateral	767	5	0.7	0.05†

*$p < 0.001$, compared with midline episiotomy, χ^2.
†$p < 0.001$, compared with no episiotomy, χ^2.

Finally, fourth-degree lacerations and their relation to episiotomy were examined separately (Table III). Clearly, midline episiotomy was associated with a high risk for fourth-degree laceration. The total number of lacerations after mediolateral episiotomy (five cases) and after no episiotomy (nine cases) was too small to support a multivariate analysis of the role of other risk factors.

Comment

The results show that several factors can be used to identify the patient at risk for perineal laceration with operative vaginal delivery and suggest potential strategies to reduce that risk.

Factors such as parity, second-stage arrest, station, and ethnic group are clearly beyond the control of the operator but should be known and considered before any operative intervention. Nulliparity is well known to be an important risk factor for perineal laceration in spontaneous deliveries.[6-9, 15] This effect is probably a result of the relative inelasticity of the nulliparous perineum. Inadequate time for perineal stretching probably explains the present observation that operative deliveries from stations higher than the outlet had increased risk for lacerations. Racial differences in perineal anatomy may also contribute to laceration. Green and Soo Hoo[6] found that Asian women had a high risk for perineal laceration in spontaneous deliveries and suggested that this may be caused by a relatively short perineal body in these women.

Of the factors under the operator's control, the choice of episiotomy is clearly the most important. In some operative deliveries the perineum is sufficiently distensible to allow delivery without episitiotomy, and this strategy may lower the risk for laceration.

The propensity of midline episiotomies to extend into the sphincter and the mucosa is well known.[10] A policy of routine mediolateral episiotomy for all operative deliveries would certainly result in fewer lacerations. However, mediolateral episiotomy is not entirely benign. It is widely believed that mediolateral episiotomies bleed more than midline episiotomies and heal with more complications. Dyspareunia is reported up to a year after mediolateral episiotomy.[16, 17] Although it is not clear whether mediolateral episiotomy is "worse" than a third- or fourth-degree laceration, the complications of laceration such as sphincter incontinence and fistula formation[1-5] are more likely to be permanent and potentially disabling than complications of mediolateral episiotomy. Thus we believe that selective use of mediolateral episiotomy is justified in a patient with several risk factors for laceration, especially nulliparity. If the patient has an epidural catheter in place during delivery, a dose of epidural narcotic may greatly alleviate the increased pain during the first postoperative day.

Vacuum extraction has been consistently found to result in less maternal soft tissue trauma than forceps delivery.[18-22] However, infants delivered with the vacuum extractor may have a higher incidence of cephalhematoma[18, 22-26] and hyperbilirubinemia that requires phototherapy.[18, 21, 26] It is debatable whether the small decreased risk to the mother justifies the routine use of vacuum extraction instead of forceps. The choice of instruments depends not only on a consideration of the risk of perineal laceration but also on the skills and training of the operator, the availability of the instruments, and other obstetric factors.

The effect of anesthesia on the risk for perineal laceration is incompletely understood. Studies of spontaneous deliveries have not detected a consistent effect of epidural anesthesia on the rate of lacerations.[6, 7, 15] Our results suggest either that local anesthesia increases the risk or that conduction anesthesia decreases the risk. It is possible that local infiltration somehow weakens the sphincter capsule and predisposes it to rupture during operative delivery. More likely is the possibility that conduction anesthesia relaxes the perineal musculature and provides a degree of protection. Regardless of the mechanism, these results suggest that epidural or saddle anesthesia should be considered before operative vaginal delivery if time and the fetal condition allow it.

The finding that birth weight and gestational age did not influence the risk of laceration was surprising and suggests that the instrument itself is the important factor influencing risk. The finding that deliveries performed by residents, after the other factors were con-

trolled, were no more likely to result in laceration than deliveries by faculty was also surprising and suggests that training and experience provide little protection to the perineum. Standard texts of operative obstetrics offer little guidance with regard to perineal management during forceps deliveries except to suggest that the blades be removed early and that a modified Ritgen maneuver be used to keep the fetal head flexed. Thompson[27] suggested that flexion could be maintained by active retraction of the anterior vaginal introitus but apparently found the technique unsatisfactory for forceps deliveries. Thacker and Banta[28] reviewed the diversity of opinions regarding where, when, and how pressure should be applied during delivery of the head and could not find a consensus.

It has been suggested that lithotomy position increases the propensity for laceration in spontaneous deliveries.[6, 12, 15] For operative delivery, the only reasonable alternative to lithotomy position is use of a birthing chair. However, randomized trials of birthing chairs for spontaneous deliveries have shown only minimally decreased rates of perineal laceration but substantially higher rates of postpartum hemorrhage.[29, 30]

The prevention of third- and fourth-degree perineal lacerations requires that the operator identify the patient at risk. Nulliparity, second-stage arrest, occipitoposterior position, nonoutlet station, and Asian race are significant risk factors. Mediolateral episiotomy, conduction anesthesia, and vacuum extraction might reasonably be considered for high-risk patients. Well-designed prospective trials are needed to determine the value of these interventions in prevention of perineal lacerations.

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A comparison of tocolysis with nifedipine or ritodrine: Analysis of efficacy and maternal, fetal, and neonatal outcome

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Nifedipine, a dihydropyridone calcium entry blocker, has been used with increasing frequency in the treatment of preterm labor. We studied 66 patients in this prospective, randomized trial to evaluate the efficacy and maternal, fetal, and neonatal outcome associated with tocolysis with nifedipine or ritodrine. Delivery was delayed for 48 hours, 7 days, and until the thirty-sixth week of gestation in 84%, 70%, and 41%, respectively, of patients in the nifedipine group, compared with 72%, 63%, and 52% of patients in the ritodrine group (difference not significant). Maternal side effects were more common and more serious in the group of patients who received ritodrine compared with those who received nifedipine (18 of 38 versus 5 of 38, $p < 0.01$); however, fetal and neonatal outcome appeared to be similar when the groups were compared. On the basis of this study, it appears that tocolysis with either nifedipine or ritodrine is equally efficacious; however, maternal side effects are less common with nifedipine treatment. We conclude that nifedipine may have a role in the treatment of preterm labor but suggest further careful evaluation of this agent before it is considered for routine clinical use. (AM J OBSTET GYNECOL 1990;163:105-11.)

Key words: Nifedipine; ritodrine; labor, premature; tocolysis

β-Adrenergic receptor–blocking agents, specifically ritodrine, are the most commonly used drugs for the treatment of preterm labor.[1] Despite the widespread use of β-adrenergic tocolytic drugs for the past decade, a variety of serious and occasionally fatal side effects is continually encountered when patients are treated with these agents.[2, 3]

Nifedipine, a dihydropyridone calcium entry blocker, may represent an attractive therapeutic alternative to the β-adrenergic agents. This agent has well-known relaxing effects on the myometrium and has been used with increasing frequency in the pharmacologic treatment of preterm labor. The findings from several preliminary nonrandomized trials describing the clinical use of nifedipine in human beings suggest that this drug may be more efficacious than ritodrine with few apparent maternal or fetal side effects.[4, 5] However, previous studies may not have allowed for a rigorous comparative evaluation of this agent. Moreover, in some animal studies the administration of nifedipine has been associated with decreases in uterine blood flow and the occurrence of fetal hypoxia and acidosis.[6, 7]

Experience to date is limited with regard to the clinical use of nifedipine in humans, and questions still remain concerning the tocolytic effectiveness, the incidence of maternal and fetal/neonatal side effects, and the outcome of exposed neonates. To address these important issues, we designed this prospective, randomized study and compared tocolysis with nifedipine to tocolysis with ritodrine, currently the accepted standard and the only agent approved by the Food and Drug Administration.

Material and methods

Patients with preterm labor that occurred between 20 and 36 completed weeks of gestation who were seen in the Stanford University Hospital or Santa Clara Kaiser Hospital delivery rooms between July 1984 and August 1987 were eligible for enrollment into the study. Preterm labor was defined as regular uterine contractions at a frequency of eight or more per hour with a documented change in cervical dilatation or effacement before 36 completed weeks' gestational age. Informed consent, as approved by the Stanford University Committee for Protection of Human Subjects in Research and the Kaiser Permanente Human Subjects' Committee, was obtained from each patient. After preterm labor was diagnosed and written consent had been obtained, the assignment group was determined by

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opening a sequentially numbered, sealed envelope, randomized by the use of a random number table with the patients stratified according to cervical dilatation (≤2 cm and >2 but ≤4 cm) and whether the patient had intact or ruptured membranes. Documented cervical change was recognized as a progressive increase in cervical dilatation, or percent effacement, or both that occurred between separate digital or speculum examinations by the same physician in patients with intact or ruptured membranes, respectively. Patients with the following maternal factors were excluded: known tocolytic exposure during the current pregnancy, diabetes, hyperthyroidism, cardiac disease, severe preeclampsia-eclampsia, abruptio placentae, chorioamnionitis, multiple gestation, hydramnios, and cervical dilatation >4 cm. Fetal distress, severe intrauterine growth retardation, dead fetus, or fetal anomaly incompatible with life constituted fetal factors for exclusion.

An intravenous infusion of 5% dextrose in lactated Ringer's solution at 100 ml/hr was administered to all patients after an initial 200 ml fluid bolus. In both study groups fluid intake was thus limited to 2400 ml/24 hr, and volume of total intake and urine output was recorded. Patients had no oral intake during the initial 24 hours of therapy except that sips of water were permitted to swallow oral medications. Maternal cardiovascular and metabolic parameters were determined at frequent intervals and the maternal and fetal-neonatal disposition of nifedipine was investigated; data from patients in each of these subgroups have recently been published.[8, 9] Before and at 12 hours of treatment, an electrocardiogram was obtained from each patient. Fetal heart rate and uterine activity were monitored continuously during the study. Cervical cultures for group B β-hemolytic streptococci and *Neisseria gonorrhoeae* were obtained. The use of amniocentesis and steroid administration followed our standard practice as previously described.[10]

Nifedipine tocolysis was initiated with a 10 mg capsule given sublingually. If uterine contractions persisted after 20 minutes, a similar dose was repeated at intervals of 20 minutes, up to a maximal total dose of 40 mg during the first hour of treatment. (Twenty-six patients received four sublingual doses, five received three doses, and two patients received two sublingual doses of nifedipine). If sublingual tocolysis stopped uterine activity, then oral therapy with 20 mg of nifedipine was initiated 6 hours after the last sublingual capsule. This dose was repeated at 4- to 6-hour intervals or, if needed to continue tocolysis, occasionally at more frequent intervals.

During treatment in the ritodrine group the infusion rate was begun at 50 μg/min and increased by 50 μg/min every 15 to 30 minutes in response to continued uterine activity until uterine contractions were inhibited, 350 μg/min was reached, or unacceptable side effects developed. Thereafter the infusion rate was decreased by 50 μg/min and was then maintained at that rate for 12 hours. (If labor recurred during this interval the above sequence was repeated.) After 12 hours the infusion rate was decreased by 50 μg/min every 2 hours until 100 μg/min was reached. Oral therapy (10 to 20 mg every 4 to 6 hours) was started 30 minutes before the discontinuation of intravenous ritodrine. (During oral therapy patients received 10 mg every 4 hours or 20 mg every 4 to 6 hours.)

Patients who had recurrent preterm labor while receiving oral nifedipine or ritodrine were treated sublingually or intravenously, respectively, with the same drug to which they had been randomized. If the uterine contractions stopped, they were again given their assigned oral tocolytic agent. In addition, although it was the intent to use only a single tocolytic agent in each patient and to allow delivery if uterine contractions with progressive cervical dilatation persisted or if a maternal side effect required the discontinuation of the tocolytic agent, in 10 cases physicians caring for patients who were failing with one treatment agent switched them to the other in an attempt to prevent delivery. Because these "crossover" cases allowed us to compare whether patients might respond to the alternate tocolytic agent, they too are described.

When patients had been stable while receiving oral tocolytics for 12 to 24 hours they were transferred from the labor and delivery unit to an antepartum ward, and were then discharged home after 1 to 2 additional days of hospitalization, during which activities consisted of bed rest with bathroom privileges. As outpatients they were seen at weekly intervals and had frequent evaluation of the cervical state and reenforcement of the educational instructions concerning the signs and symptoms of preterm labor. Ambulatory home uterine contraction monitoring was not used.

In both the nifedipine and ritodrine treatment groups, our goals for tocolysis were to delay delivery for 48 hours in patients with ruptured membranes, and through 36 completed weeks of gestation in patients in whom the membranes were intact. Therapy was considered successful when, in each respective group, delivery was delayed for these intervals. In patients with intact membranes we also evaluated the ability of these drugs to postpone delivery for 1 week. Treatment failure was said to exist if, despite maximal dosages of nifedipine or ritodrine, uterine quiescence could not be achieved and delivery occurred, or if because of continued uterine contractions and cervical dilatation, a patient was switched to the alternative therapy before the described intervals of tocolysis had been attained. If a patient had a significant maternal side effect that the attending obstetrician judged to necessitate discontinuation of the medication or change to the alternative

Table I. Maternal factors of study patients randomly selected to receive nifedipine or ritodrine tocolysis

Classification	*Nifedipine*	*Ritodrine*
Age (yr)*	26.7 ± 5.2	25.7 ± 4.9
Gestational age (wk)*	30.7 ± 3.1	30.8 ± 2.4
Parity		
0	17/33	19/33
>0	16/33	14/33
Cervical dilatation (cm)		
≤2	27/33	27/33
>2,≤4	6/33	6/33
Cervical effacement (%)*	60.0 ± 22.0	67.2 ± 24.7
Premature rupture of membranes	8/33	6/3
Betamethasone use	29/33	30/33

*Mean ± SD; none of these significantly different by Student's t test or χ^2 analysis, where appropriate.

Table II. Delay in delivery*

	48 hr		*7 days*		*36 wk*	
Tocolytic agent	*No.*	*%*	*No.*	*%*	*No.*	*%*
Nifedipine	27/32	84	16/23	70	9/22	41
Ritodrine	23/32	72	17/27	63	14/27	52

*No intergroup comparisons were statistically significant by χ^2 analysis.

therapy, or if spontaneous rupture of membranes developed, a treatment failure was said to have occurred.

Information concerning side effects and their management was carefully recorded about each patient by the physician or nurse caring for the patient. Treatment of side effects was individualized. In most instances expectant management or symptomatic treatment was sufficient. A reduction in the amount or interval of administration of the therapeutic agent was usually helpful in treating patients who complained of nausea and vomiting or chest pain. In some patients, however, persistent and worrisome side effects prompted the treating physician to discontinue tocolytic therapy.

Statistical analysis was performed with the Student's t test, χ^2 analysis with Yate's correction, one-way analysis of variance, or Fisher's exact test where appropriate to determine significance ($p < 0.05$).

Results

Sixty-six patients were enrolled in the study; 33 were randomized to nifedipine treatment and 33 to ritodrine. It was unknown at the time of randomization and initial hospital care that two patients in each group had received a single subcutaneous 0.25 mg dose of terbutaline before transfer to the study institutions. They are included in this evaluation of tocolytic success and maternal and fetal/neonatal outcome.

Patients in the two treatment groups were first compared for various factors that could contribute to success of tocolysis and maternal or fetal/neonatal outcome. Table I shows that there was no significant difference in maternal age, parity, gestational age, cervical dilatation or effacement, use of steroids, or incidence of ruptured membranes when the two groups were compared.

The overall duration of successful therapy can be noted in Table II. Use of nifedipine delayed delivery for 48 hours in 84% (27/32) of the patients. (One patient in the nifedipine treatment group who had intact membranes and whose labor was successfully arrested for 24 hours requested withdrawal from the study and was treated with terbutaline. Terbutaline tocolysis failed and she was delivered of a previable infant.) Of note, tocolysis was successful in six of the eight patients with spontaneous rupture of membranes. As noted in the Material and methods section, in patients with spontaneous rupture of membranes tocolysis was not attempted beyond 48 hours, and after the cessation of tocolytic therapy delivery ensued in all patients within 7 days. Two other patients were withdrawn from further analysis of efficacy in the nifedipine group. In one patient with intact membranes and oligohydramnios, tocolysis was used only for 48 hours to administer steroids and was then discontinued to allow delivery. The second patient was withdrawn from further analysis of efficacy because after 36 days of successful tocolysis, she failed to refill her prescription and came to the hospital 1 day later in advanced labor. Therefore tocolysis had been attempted in 23 patients at 7 days and in 22 patients by 36 weeks. Delivery was delayed in 16 (70%) of 23 patients at 7 days and beyond 36 weeks in 9 (41%) of the 22 patients. In the group of patients randomized to receive ritodrine, tocolysis was success-

Table III. Treatment failures and the alternate agent to delay delivery an additional 48 hours

Initial agent	*Alternate agent used*		*No alternate agent*	
	No.	*Delay ≥48 hr*	*No.*	*Delayed ≥48 hr*
Nifedipine (n = 15)	5*	3/5	10	0/10
Ritodrine (n = 16)	5*	3/5	11	0/11

*Delivery was delayed beyond 48 hours more frequently in those patients in whom the alternate agent was used when compared with those in whom no alternate agent was used ($p<0.001$, Fisher's exact test of probability).

Table IV. Side effects associated with nifedipine and ritodrine therapy

	Nifedipine	*Ritodrine*
Total No. of patients receiving drugs*	38	38
Total No. with side effects†	5	18
Side effects		
Chest pain–tightness	1	8
Nausea or vomiting	0	7
Palpitations	0	2
Flushing	2	0
Headache	2	2
PVCs, SVT	0	2
Pulmonary edema	0	1

PVCs, Premature ventricular contractions; *SVT,* supraventricular tachycardia.

*Includes the 33 patients randomly assigned to each treatment and the additional five "crossover" patients who were exposed to the alternate tocolytic agent.

†Some patients had more than one side effect. ($p<0.01$, Fisher's exact test of probability).

ful for 48 hours in 72% (23/32). (A single patient with spontaneous rupture of membranes in the ritodrine group was withdrawn from the study because she was found to have a mature lecithin/sphingomyelin ratio and tocolysis was discontinued and delivery subsequently occurred.) Of the five remaining patients with spontaneous rupture of membranes in the ritodrine group, tocolysis was successful in two, then the medication was discontinued and delivery occurred within 1 week. Twenty-seven patients remained in the ritodrine treatment group; delivery was delayed for at least 1 week in 17 (63%) and until at least 36 weeks in 52% (14/27). There were no statistically significant differences between the two treatment groups when compared at the three durations of tocolysis.

Treatment failures occurred in 15 patients in the nifedipine treatment group (Table III). In five instances crossover therapy with intravenous and then oral ritodrine was attempted by the attending physician; tocolysis was accomplished in three cases with a further prolongation of pregnancy of 16, 35, and 60 days. Ritodrine tocolysis was not successful in the other two cases. In the remaining 10 cases no alternate agent was used and delivery occurred in all within 12 hours. In the ritodrine group there were 16 treatment failures. Crossover treatment with sublingual and then oral nifedipine was attempted in five patients, and delivery was delayed in three patients for 50, 68, and 84 days. When no alternate agent was used, delivery occurred in the remaining 11 patients within 12 hours. Overall, patients in whom crossover therapy with the alternate agent was attempted had a significantly greater chance of delaying delivery beyond 48 hours ($p < 0.001$) when compared with patients in whom the alternate agent was not used.

The maternal side effects in the two treatment groups are compared in Table IV. For the purpose of this enumeration, the five "crossover" patients from each group have been included in both their original group and their alternate drug group. Side effects were tabulated according to the drug the patient was taking when they occurred. Side effects occurred more commonly in the ritodrine group ($p < 0.01$). In the ritodrine treatment group chest pain and nausea or vomiting were the most common side effects. Although in most instances a reduction in the infusion rate of ritodrine and symptomatic treatment alleviated these complaints, in three patients it was necessary to discontinue the infusion. One of these three patients had multifocal premature ventricular contractions; the second had supraventricular tachycardia successfully treated with intravenous verapamil after failure of carotid sinus massage and the Valsalva maneuver; and in the third patient, despite a normal electrocardiogrm and reduced infusion rate, the persistent and oppressive chest pain was clinically judged to require discontinuation. In the nifedipine group headache and flushing were the most common complaints. Chest pain and pressure associated with pyrosis was encountered in one patient in the nifedipine group and was successfully treated with ant-

Table V. Perinatal outcome for fetuses exposed only to nifedipine or ritodrine and those sequentially exposed to both agents

	Nifedipine	*Ritodrine*	*Both drugs*
Infants (No.)	28	28	10
Gender			
Male	12	10	7
Female	16	18	3
IUFD	0	0	1
Neonatal death	2	0	0
RDS	4	2	2
Ventilator treatment			
At 2 wk	0	0	2
At 4 wk	0	0	2
Intraventricular hemorrhage	2	1	1
Apgar score <7			
1 min	5	8	3
5 min	2	3	3
Birth weight (gm, mean ± SD)	2228 ± 880	2467 ± 901	2080 ± 1099

*IUFD,*Intrauterine fetal death; *RDS,*respiratory distress syndrome.
No intergroup comparisons were statistically significant (χ^2 analysis, Fisher's exact test, and analysis of variance.

acids and elevation of the head of the patient's bed. Of the 10 patients who sequentially received both tocolytic agents, two had side effects. One patient who had headaches while receiving nifedipine also had headaches while receiving ritodrine but in addition had nausea and vomiting. In an additional patient who was receiving intravenous ritodrine at a gestational age of 26 weeks, recurrent uterine contractions with progressive cervical dilatation occurred. Pulmonary edema was also diagnosed. She was treated with morphine sulfate, oxygen, and diuretics and switched to nifedipine; however, continued attempts at tocolysis were unsucessful.

Outcome data for the neonates exposed in utero to only nifedipine and ritodrine, as well as those sequentially exposed to both agents, are detailed in Table V. There were no significant differences when intergroup comparisons were performed on outcome parameters. There was a single fetal demise in the study. In this pregnancy tocolysis was initially accomplishd with nifedipine, but failure occurred after 4 days and intravenous and then oral ritodrine tocolysis was attempted and successful. Because of ultrasonographically suspected fetal anomalies at the time of initial evaluation, amniotcentesis had been performed for cytogenetic studies. Sixteen days later the patient presented after failure of ritodrine therapy with fetal demise; the then completed cytogenetic studies revealed trisomy 13. Two neonatal deaths occurred in the nifedipine group. In one case the patient, as described above, requested withdrawal from the study after 24 hours of successful tocolysis with nifedipine and was subsequently treated with terbutaline and within 15 hours was delivered of a 22-week gestation with Apgar scores of 1 at 1 minute and 1 at 5 minutes that died in the first hour of life. The second neonate, a male delivered at 28½ weeks, had Apgar scores of 2 and 6 at 1 and 5 minutes, respectively, died at 11 days of age. The neonatal course was complicated by severe respiratory distress syndrome and the rapid development of pulmonary interstitial emphysema. Obstetric complications, in addition to continued uterine contractions, included a partial placental previa with active bleeding, bulging chorioamniotic membranes with a funic presentation, and the need for an urgent cesarean section. The infant's cord pH was 7.38 at the time of delivery. There was no evidence of hypovolemia or of any possible cardiovascular effects of nifedipine. The neonatal evaluation concluded the cause of death was unrelated to nifedipine administration and attributed it to severe respiratory distress syndrome and pulmonary interstitial emphysema, with hypoxemia refractory to mechanical ventilation and pharmacologic cardiopulmonary intensive care. The two neonates in the group exposed to both drugs, who had respiratory distress syndrome and required ventilator treatment at 2 and 4 weeks after delivery, were each delivered after ritodrine therapy and subsequent attempted tocolysis with nifedipine had failed. The neonates with intraventricular hemorrhage all had grade I hemorrhages.

Comment

We have demonstrated that nifedipine appears to be a comparable but not superior tocolytic agent when compared with ritodrine hydrochloride. Two previous studies have reported on the tocolytic efficacy of nifedipine when used as a primary agent. Ulmsten[4] studied 28 patients in preterm labor (eight of whom were also hypertensive). All patients had previously uncomplicated singleton gestations between 27 and 33 weeks, two or more uterine contractions in 10 minutes, and an effaced cervix that was not dilated >4 cm. Treatment was initiated with 30 mg of nifedipine orally, followed by 20 mg orally three times a day for 3 days, then twice a day thereafter. Tocolysis was reported to

be successful for 72 hours in 80% of the patients. In a second study by Read and Wellby,[5] patients were assigned in a nonrandom format to receive nifedipine, ritodrine, or no tocolytic treatment. Patients were included for the treatment of preterm labor if there was a contraction frequency of at least once every 10 minutes, the membranes were intact, and the cervix was not dilated beyond 4 cm. Nifedipine was administered as a single course of 30 mg orally followed by 20 mg orally at 8-hour intervals for 3 days. The authors reported a significantly greater percentage of "postponement of delivery" (delay beyond 48 to 72 hours) when patients treated with nifedipine (15 of 20, 75%) were compared with patients treated with ritodrine (9/20, 45%) or untreated patients (7/20, 35%). In these two studies there was no description of success at delaying delivery for longer intervals. Our study design was somewhat different from those used in the previously mentioned reports in that our definition of preterm labor was more stringent, we included patients with spontaneous rupture of membranes, and because initial tocolysis for patients in the nifedipine group used incremental doses of sublingaul nifedipine to obtain more rapid serum concentrations.[9] In addition, we chose to evaluate the shortest interval of success of tocolysis as 48 hours instead of 72 hours because this is the amount of time we attempt to gain for the fetus in utero to enhance fetal lung maturity with glucocorticoid administration. Despite the differences in study designs, the combined success we report in delaying delivery for both 48 hours and 1 week after the initiation of therapy is very similar to the rate of tocolytic success and "postponement of delivery" reported by Ulmsten[4] and Read and Wellby,[5] respectively. We cannot confirm the findings of Read and Wellby[5] with regard to the superiority of nifedipine when compared with ritodrine. In our study no significant differences were demonstrated between treatment groups when success of tocolysis was compared for any of the three intervals at which delays in delivery were evaluated. Additionally, the proportion of patients in this report who achieved 36 completed weeks' gestational age when either nifedipine or ritodrine was used is similar to the proportion of patients recently reported by Wilkens et al.[11] who were delivered after 37 weeks' gestation after aggressive treatment with ritodrine, magnesium sulfate, or both.

Our findings also demonstrate that nifedipine treatment may be useful to achieve delay of delivery in patients in whom a treatment failure has occurred with ritodrine and that the converse is true as well. Although the patients in whom crossover therapy was attempted were not randomly selected, it appears that they had a significantly greater chance of having gestation prolonged an additional 48 hours when compared with patients who received no further treatment. Preterm labor is probably a syndrome of disorders with different causes and associated pertubations of the mechanisms responsible for regulating uterine contractility. Although the regulation of uterine contractility is complex and incompletely understood, it is believed that β-adrenergic and calcium channel-blocking agents each act through a different cellular mechanism to achieve uterine quiescence.[12] Consequently, it should not be surprising that both nifedipine and ritodrine may, because of their different sites of tocolytic action, be effective when used after a treatment failure of the other agent.

When a tocolytic agent is chosen, an important consideration beyond efficacy is the possible occurrence of maternal or fetal side effects. Our findings document a greater incidence and severity of maternal side effects in patients in the ritodrine group when compared with patients in the nifedipine group. The side effects that occurred with ritodrine usage were similar in variety and type to those previously reported.[2, 11] When chest pain occurred, despite the fact that a reduction in the infusion rate of ritodrine usually ameliorated this symptom, in three patients discontinuation of the infusion was necessitated. We[13] and others[2, 3, 11] have previously reported that there appears to be a small proportion of patients who do not tolerate β-adrenergic therapy because of the occurrence of cardiac symptomatology. Nausea or vomiting was the next most frequently encountered side effect in our study. Caritis et al.[14] reported the same incidence of this side effect, whereas Wilkens et al.[11] reported this finding less frequently. We encountered few side effects associated with nifedipine usage. The proportion of patients who complained of headaches was similar to that reported by Ulmsten[4]; however, we encountered less flushing, perhaps because of a difference in treatment regimens. Read and Wellby[5] noted that troublesome side effects occurred much more commonly in the patients receiving ritodrine when compared with those receiving nifedipine or no therapy. Neither Ulmsten[4] nor Read and Wellby[5] reported any serious maternal side effects in patients treated with nifedipine.

None of the variables of perinatal outcome that we assessed appeared to be affected differently by either treatment regimen or when the drugs were used sequentially. Ulmsten[4] reported two neonates with Apgar scores less than 7, encountered no perinatal deaths, and found appropriate birth weights in the neonates. Read and Wellby[5] also reported similar Apgar scores in the nifedipine and ritodrine groups and no perinatal deaths. In a recent study by Adam et al. (Adam K, Kirshon B, Lee W, Spillman T, Johnson D, Mauer MB, Cotton DB. Acid-base balance in the human fetus during nifedipine therapy [Abstract 209]. In: Proceedings of the Ninth Annual Meeting of the Society of Perinatal Obstetricians, New Orleans, Louisiana, February 2-4, 1989) eight patients in preterm labor were treated with 30 mg of nifedipine orally, followed in 4 hours by an additional 20 mg oral dose. Six hours after the initial

dose of nifedipine, the maternal mean arterial pressure was compared with baseline, and umbilical cord blood sampling was performed to evaluate fetal acid-base status. These investigators demonstrated that the maternal mean arterial pressure did not change and there was no evidence of fetal acidosis or hypoxia.

Despite the favorable fetal-neonatal outcomes to date with use of nifedipine in human gestations, the animal data documenting maternal and fetal hemodynamic and associated cardiorespiratory responses have reported variable effects in different species; some of the findings provide reason for possible concern and continued careful surveillance. Veille et al.[15] studied the effects of bolus infusion of 5 to 45 μg/kg of nifedipine on uterine blood flow and maternal mean arterial pressure in pygmy goats; there was no significant change in uterine blood flow and only an immediate and transient fall in mean arterial pressure. Conversely, Ducsay et al.[6] and Harake et al.[7] investigated the effects of nifedipine administration in pregnant rhesus monkeys and ewes, respectively, and reported decreases in maternal mean arterial pressure and uterine blood flow with associated fetal hypoxemia and acidosis. Harake et al.[7] believe that decreases in uterine blood flow occur only with significant decreases in maternal mean arterial pressure and that fetal hypoxemia, when present, is most likely related to a fall in uterine blood flow. It is thus possible that adverse fetal hemodynamic and cardiorespiratory effects have not been demonstrated in human pregnancies when nifedipine is used because only minimal changes in maternal hemodynamics occur.[4, 5, 8]

We have demonstrated that the tocolytic efficacy of nifedipine appears to be comparable with but not superior to that associated with the use of ritodrine. We have also provided the initial documentation that nifedipine can be used to delay delivery in patients with spontaneous rupture of the membranes. In addition, nifedipine may successfully delay delivery if ritodrine tocolysis fails, and the converse was also found. Maternal side effects occurred less frequently when nifedipine was used. The perinatal outcome indicated no differences between treatment groups; however, caution must be exercised in the interpretation of this information. Despite over 3 years of patient enrollment, our study consisted of a relatively small sample size and therefore the possibility of a type II or beta error exists. Although the power of our study was less than the often accepted 80%, assuming the outcome variable proportions remain unchanged, a study population of more than 1000 patients would be required to be certain the null hypothesis is not accepted when incorrect.

On the basis of this work and previous investigations by us,[8, 16] Adams et al., and others,[4, 5] it appears that nifedipine may have a role in the therapeutic armamentarium for the treatment of preterm labor. It may be especially useful if it is necessary to minimize maternal side effects and avoid significant alterations in cardiovascular and metabolic parameters or if a patient has a treatment failure with a β-adrenergic agent. Because knowledge concerning the use of nifedipine as a tocolytic agent in human pregnancy and its possible maternal and fetal-neonatal side effects is still nascent, we believe nifedipine should only be used after obtaining informed patient consent, preferably as part of a prospective, randomized investigative trial.

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Discrepancy in the diagnoses of hydatidiform mole by macroscopic and microscopic findings and the deoxyribonucleic acid fingerprint method

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Ten cases of hydatidiform mole were analyzed by the deoxyribonucleic acid fingerprint method. Deoxyribonucleic acid samples were prepared from hydatidiform mole tissue of hydatidiform mole and maternal and paternal blood. A case of partial hydatidiform mole diagnosed by histologic findings was revealed to be complete hydatidiform mole by deoxyribonucleic acid fingerprinting. (AM J OBSTET GYNECOL 1990;163:112-3.)

Key words: Hydatidiform mole, DNA fingerprint, androgenesis

Gestational trophoblastic disease has been classified by international committees such as the Union Internationale Contre le Cancer, World Health Organization, and the International Federation of Gynecology and Obstetrics. The classification of noninvasive hydatidiform mole included complete hydatidiform mole and partial hydatidiform mole. These have been macroscopically diagnosed. However, it has been recommended that histologic classification should be carried out. The deoxyribonucleic acid (DNA) fingerprint method is available for personal identification and for determination of true parenthood.[1] Inasmuch as complete hydatidiform moles are of androgenetic origin but partial hydatidiform moles are not and are a result of a chromosomal anomaly of mainly a triploid karyotype, the DNA fingerprint method should be useful in distinguishing partial hydatidiform moles from complete hydatidiform moles. It is important to accurately diagnose complete hydatidiform moles and partial hydatidiform moles because of the incidence of persistent trophoblastic disease.

We have studied 10 cases of hydatidiform mole including three cases of partial hydatidiform mole. DNA samples were prepared from the molar tissue and parental blood, and DNA fingerprinting was performed. Hydatidiform moles were analyzed by DNA fingerprinting and the diagnoses were compared with macroscopic and microscopic diagnoses. A case of partial hydatidiform mole diagnosed by histologic findings was revealed to be complete hydatidiform mole by DNA fingerprinting.

Case report

A 28-year-old gravida 1, para 1 woman underwent curettage at 12 weeks' gestation under the diagnosis of hydatidiform mole. The diagnosis was partial hydatidiform mole macroscopically and microscopically (Fig. 1). The hydropic tissue was separated from nonhydropic tissue and collected, and the DNA fingerprint was performed (lane 1, father; lane 2, mother; lane 3, hydropic tissue; and lane 4, nonhydropic tissue in Fig. 2). The bands of the DNA fingerprint of hydropic tissue were almost the same as those of the paternal gene, but not of parental origin. Because the urinary human chorionic gonadotropin titer did not go down in 1 month after evacuation of the mole and lung metastasis was identified by roentgenogram of the chest, the patient was treated by three courses of methotrexate (one course, methotrexate 10 mg/day × 5 days). The urinary human chorionic gonadotropin level went down to the leuteinizing hormone level 2 months after treatment.

Comment

The case was thought to be partial hydatidiform mole by macroscopic and microscopic methods. However, it was indicated by DNA fingerprinting to be complete hydatidiform mole. It might be a dizygotic conception with a complete hydatidiform mole and an abortion. Such a twin pregnancy was reported by chromosomal analysis.[2] We thought that the case should be dealt with

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Fig. 1. Hydropic chorionic villi, almost normal chorionic villi, and proliferation of trophoblasts in this case. Hematoxylin-eosin stain. (Original magnification ×6).

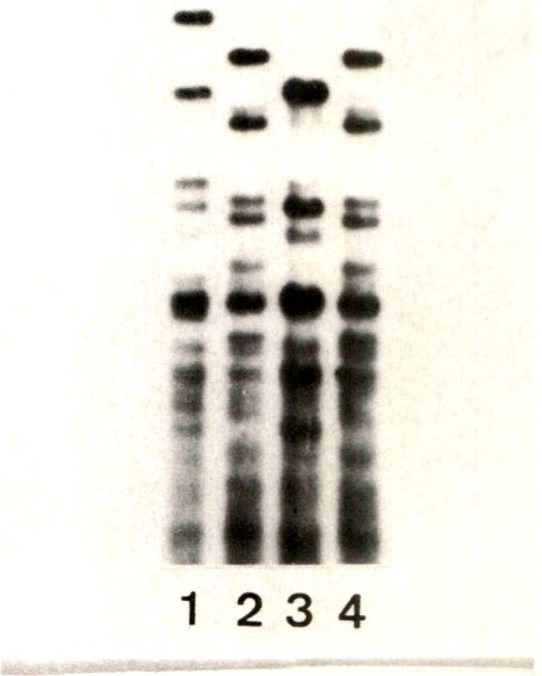


Fig. 2. DNA fingerprints of case. Lane 1, father; lane 2, mother; lane 3, hydropic tissue; and lane 4, nonhydropic tissue.

as complete hydatidiform mole. In fact, it was found to be persistent trophoblastic disease and was treated by chemotherapy.

The merits of DNA fingerprinting are that materials can be stored easily and the experiments can be made at any time, which is not possible by chromosomal analysis. Also, DNA fingerprinting can be available for the classification of complete hydatidiform mole and partial hydatidiform mole.

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Autogenic masculinization

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We present a case in which self-treatment of lichen sclerosus with large doses of topical testosterone resulted in marked masculinization and may have caused secondary amenorrhea. These changes have not previously been reported as side effects of topical testosterone use. (AM J OBSTET GYNECOL 1990;163:114-6.)

Key words: Lichen sclerosus, testosterone therapy

Lichen sclerosus is a vulvar dystrophy associated with pruritus and diffuse whitish change in the vulvar skin. The skin may appear thin and atrophied or contain fissures. Histologically, the epithelium is thinned with loss of rete ridges and may be noted to have hyperkeratosis at the surface level. The standard treatment approach is topical application of 2% testosterone propionate in petrolatum ointment. The amount needed for each application to the vulvar tissues usually represents 8 to 10 mg of testosterone. The usual regimen of therapy is an application twice a day for the initial period of 6 weeks or until symptoms of pruritus resolve. The dosage is tapered, if the drug is effective, to a maintenance application as infrequently as twice a week. Effectiveness is reported to be high and side effects minimal. In this case report the patient was using up to 60 mg of topical testosterone on a daily basis for a prolonged period of time.

Case report

The patient, a 27-year-old nulligravid woman, gave a history of having lichen sclerosus et atrophicus on the basis of a biopsy done more than 1 year previously at another institution. She had been placed on a regimen of topical testosterone therapy. Laboratory values from March 1988 at the University of Michigan Medical Center included follicle-stimulating hormone 5.6 MIU/ml, luteinizing hormone 2.9 mIU/ml, and estradiol 38 pg/ml. She was advised to continue topical testosterone twice weekly.

She presented to the Infertility and Endocrinology Clinic in the Department of Obstetrics and Gynecology on June 13, 1988, for evaluation of amenorrhea and lichen sclerosus. A complete history was obtained and a physical examination was done at that time.

This 27-year-old nulligravid woman underwent uneventful menarche at age 12. She had monthly cycles with 3 to 4 days of menstrual flow. She used a variety of oral contraceptives from age 18 to age 26. She discontinued these in June 1987. She noted two spontaneous menses after discontinuing the oral contraceptives but had her last normal menstrual period in September 1987. She noted 2 days of spotting in January 1988 and 3 days of spotting just before her clinic visit in June 1988.

The patient was a graduate student in biology and had been mixing her own testosterone ointment. Although she had been placed on a standard dosage regimen more than 1 year before she was seen, she had been self-treating with this homemade testosterone ointment, topically applying an estimated dosage of 7.5 mg seven to eight times a day for at least 8 months. She complained of painful clitoral adhesions. She noted hot flashes and night sweats for 1 year but denied acne, hirsutism, temporal balding, breast atrophy, or weight changes. Deepening of her voice had occurred since she had been using the testosterone. She had recently begun using topical vitamin A and tapering the testosterone usage. The patient was not sexually active.

Physical examination revealed height 60½ inches, weight 93 pounds, and blood pressure 118/80 mm Hg. There was no thyromegaly. Her voice was deep. She had no facial or chest hair. The breast examination revealed small breasts with no masses, tenderness, or galactorrhea. There was no organomegaly on abdominal examination. On pelvic examination there was increased hair growth on the inner legs and upper thighs. The clitoris was enlarged, measuring 2 cm (previous size had not been documented). Some periclitoral adhesions were present along with minimal hypertrophic changes of the vulvar skin. The introitus was nulliparous, and the cervix was without lesions. The uterus was small and retroverted, and both ovaries were palpable and not enlarged.

The patient had begun taking basal body temperature 24 days before she was seen in June 1988. She had a biphasic chart with a 6-day temperature elevation

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before the onset of vaginal spotting, which was 3 days before she was seen in the infertility Endocrinology Clinic.

The impression at the time of the visit in June 1988 was that the patient had secondary amenorrhea and lichen sclerosus. Because of the virilization we suspected that she might have a component of polycystic ovarian disease. She was advised to discontinue the topical testosterone. Blood studies obtained were as follows: testosterone 11.15 ng/ml (normal 0.24 to 0.66 ng/ml), thyroid-stimulating hormone 2.1 (normal <7.0 IU/L), prolactin 7.7 ng/ml (normal 2 to 22 ng/ml), dehydroepiandroestrone sulfate 4145 ng/ml (normal 820 to 3800 ng/ml, female adult). A Papanicolaou smear was negative.

When seen again on July 13, 1988, the patient reported that she had discontinued the testosterone applications on June 15. She had 2 days of spotting on July 6 and 7. Results at repeat pelvic examination were unchanged. A repeat testosterone level was obtained on Aug. 15, 1988. It had fallen from 11.15 to 0.53 ng/ml, which was within the normal range for a female adult. When seen on Aug. 17, 1988, she was asymptomatic for lichen sclerosus and was still applying vitamin A cream topically to the vulva. She reported a normal menstrual period on July 28, 1988, lasting 3 days. Her voice was still deep. One year later she reports continued regular menstrual cycling.

Comment

Androgenic agents have many uses in modern medical therapeutics. These uses range from hormonal replacement in male patients with some hypogonadal states to stimulation of erythropoiesis in patients with aplastic anemia or chronic renal failure. Androgens also are used in the treatment of women with breast cancer.

The topical use of testosterone to treat vulvar dystrophy dates back more than 40 years. In 1945 Cinberg reported on the therapy of postmenopausal patients with vulvar pruritus. He advised the use of a bland ointment containing petrolatum alba, starch, and zinc oxide. In those patients with severely atrophic vulvar tissues he used androgenic ointments, specifically, an ointment containing 2 mg of testosterone propionate to each gram of ointment.

Richardson and Williams reported on 57 patients with vulvar dystrophy treated with topical testosterone for from 1 to 15 years. Results were classified as excellent or satisfactory in 50 patients as long as maintenance treatment was continued. Noted side effects included increased libido, increase in pubic and genitourinary hair, and a few patients with increased facial hair. Increased clitoral size also was noted but seemed to diminish after 3 to 4 years of therapy. In patients with relief of pruritus, none were willing to stop the treatment because of the side effects. Of these 57 patients, 46 were felt to have what is currently considered lichen sclerosus or a mixed dystrophy. All but five of these were improved by the topical testosterone therapy.

Friedrich[1] in 1976 reviewed the literature on lichen sclerosus and found that 130 of 137 cases of lichen sclerosus or mixed dystrophy showed improvement with topical testosterone therapy. Side effects were again thought to be minimal. Thus the regimen described by Richardson and Williams has become and remains the standard of care. Their regimen involves the application of 2% testosterone propionate ointment two to three times a day for 6 weeks or until relief of symptoms. Applications are then tapered to twice weekly. The usual application is about 10 mg of testosterone. Corticosteroids may be used initially to help reduce inflammation, if present.

There are few data in the literature on the effect of topical testosterone on serum steroid levels. In 1971 Zelle[2] reported on 15 patients treated with Richardson and Williams' treatment regimen. Nine of these patients had lichen sclerosus et atrophicus and six had hyperplastic dystrophy. Five patients had plasma androgen levels determined during active therapy and five others had 17-ketosteroid levels measured. No abnormal levels were reported. Four patients noted moderate clitoral hypertrophy and increased libido. Two patients noted only increased libido. It is not known if the patients who experienced the side effects were in the groups who had blood studies done.

In 1984, Friedrich and Kalra[3] reported on 30 women with untreated, biopsy-proved lichen sclerosus who had sex steroid hormone levels determined before initiation of topical testosterone therapy. Ten of these women had repeat levels measured at varying times in the treatment, which showed an increase in total testosterone from an average of 0.225 to 0.875 ng/ml. Dihydrotestosterone levels increased from an average of 0.07 to 0.28 ng/ml. Of the 10 patients with two hormone level determinations only one noted side effects, and those were confined to pubic hirsutism and slight facial acne. Two of the 10 noted no response to therapy despite a documented increase in serum androgen levels indicating some systemic absorption of the topical medical.

Although the diagnosis of polycystic ovarian disease was initially considered, review of the laboratory values led to the impression that she had stigmas of polycystic ovarian disease caused by exogenous androgen. Amenorrhea is one of the clinical findings in patients who have virilization caused by polycystic ovaries, some ovarian neoplasms, and exogenous androgen. The patient in this case report most likely had secondary amenorrhea in association with the dose of topical testosterone she was absorbing. The cause of the amenorrhea may have been chronic anovulation, as well as a com-

ponent of endometrial atrophy resulting from the antiestrogenic effect of testosterone. An endometrial biopsy was not done. The basal body temperature chart was biphasic at the time of presentation, and this may have reflected a spontaneous ovulation as she had already begun to taper her testosterone usage.

This case report demonstrates the effect of high-dose topical testosterone therapy. The dosages estimated to be applied to the vulvar tissues of this patient were twice the amount recommended in the acute phase of treatment and at least 15 times the usual maintenance dosage. These are dosages that have never been advocated in the literature. The resultant masculinization, as well as the markedly elevated serum testosterone level, points to the effectiveness of the vulvar skin in absorbing topical testosterone into the systemic system. These menstrual changes and the deepened voice have not been reported as side effects in previous studies regarding the topical use of testosterone by women. Discontinuation of the topical testosterone resulted in the resumption of spontaneous menstrual bleeding. The testosterone level returned to normal within 2 months. Lichen sclerosus was stable in the short-term follow-up available. Some low-dose maintenance therapy may be necessary for her to remain symptom-free. Voice changes are irreversible.

In summary, this case report stresses the importance of proper dosing with topical testosterone. Usual dosages have been associated with minimal side effects; however, excessive dosing may result in impressive masculinization and secondary amenorrhea because of the systemic absorption of the topically applied ointment.

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A complete list of references is available from the authors on request.

Vulvar ulcer of unknown etiology in a human immunodeficiency virus–infected woman: Response to treatment with zidovudine

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We report a woman who presented with an intractable vulvar ulcer of unknown etiology. Human immunodeficiency virus antibodies and a depressed CD4 lymphocyte count were the only remarkable findings. There was no evidence of syphilis, chancroid, or herpes simplex virus infection. The ulcer healed in association with treatment with zidovudine. (Am J Obstet Gynecol 1990;163:116-8.)

Key words: Vulvar ulcer, human immunodeficiency virus, zidovudine

This report describes a woman who had a refractory vulvar ulcer of unknown etiology when she was first seen. There was laboratory evidence of infection with human immunodeficiency virus (HIV), and treatment with zidovudine was associated with healing of the ulcer.

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Case report

A 34-year-old, white woman was first seen in August 1986 because of genital warts. She was born in Brooklyn, New York, and was a lifelong resident. She was employed as a data-entry clerk. She lived with her three

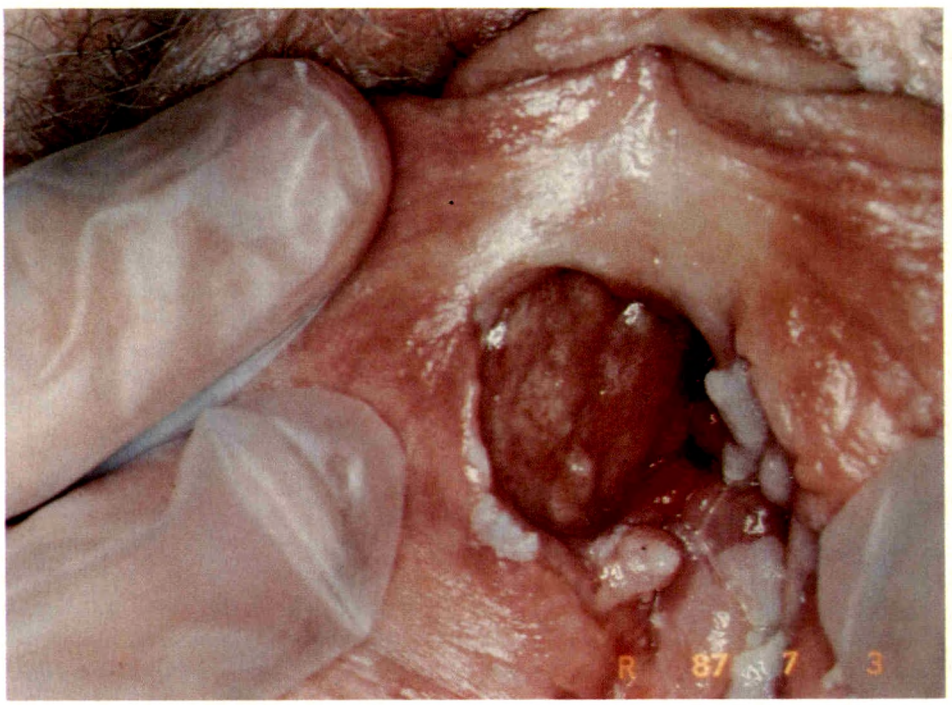


Fig. 1. Right vestibular ulcer before treatment with zidovudine (March 1987).

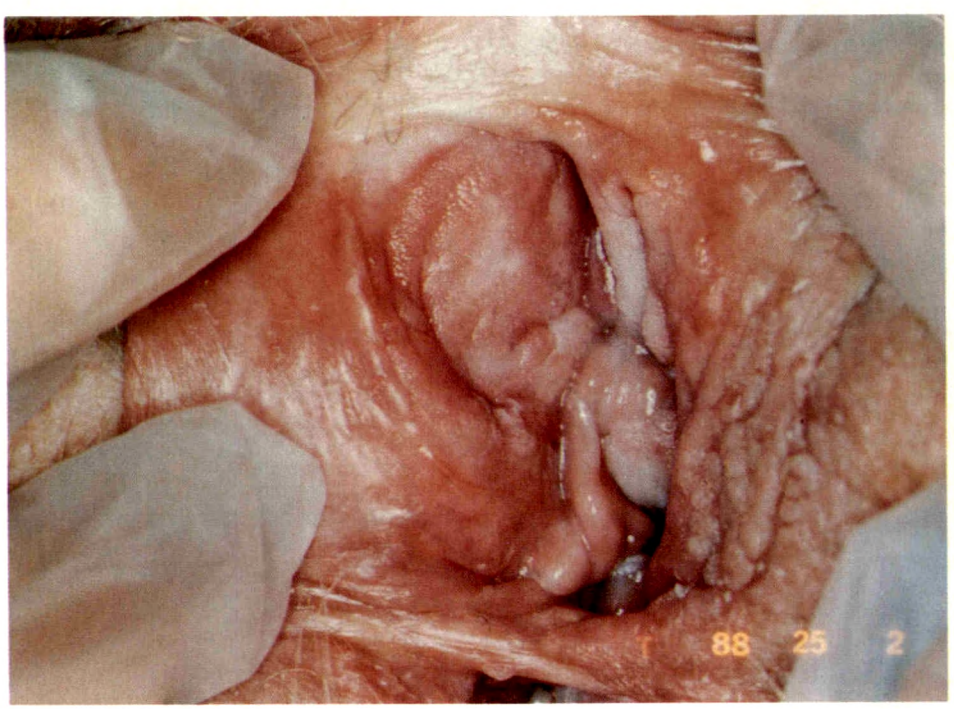


Fig. 2. Right vestibular ulcer after treatment. The ulcer has reepithelialized (February 1988).

daughters, aged 10 to 15. She had been separated from her husband for 10 years. Since the separation she had had six male sexual partners. Although the patient gave no history of illicit drug use, her husband had used drugs and died of "pneumonia" in early 1987. She had received a blood transfusion in Brooklyn, New York, in 1980 when she was treated for an ectopic pregnancy.

The genital warts were ablated with use of a laser. Subsequently she was noted to have recurrent condylomas and a painful right vestibular ulcer. She also reported recurrent painful oral ulcers that healed spontaneously. The vestibular ulcer enlarged despite treatment with erythromycin, acyclovir, ceftriaxone, and doxycycline. By March 1987 the ulcer had increased to 4 cm in size (Fig. 1). There were aphthous ulcers of the inner aspect of the left upper lip and of the right tonsillar pillar. By May 1987 the oral aphthae had healed. Another painful, smaller ulcer was noted on the left side of the perineum. The vestibular ulcer persisted.

Laboratory data included a hemoglobin of 8.9 gm/dl. The hematocrit was 28%. The white blood cell count was 5700/mm^3, with 30% lymphocytes and 69% neutrophils. Examination of a bone marrow biopsy specimen revealed only increased histiocytic activity. The serum levels of creatinine, urea nitrogen, alkaline phosphatase, bilirubin, transaminase, haptoglobin, glucose-6-phosphate dehydrogenase, and vitamin B_{12} were within normal limits. The erythrocyte sedimentation rate was 59 mm/hr. The serum iron level was 47 μg/dl with a total iron-binding capacity of 300 μg/dl. The urinalysis results were normal as were the prothrombin time and partial thromboplastin time. An electrocardiogram and results of chest radiographic examination were normal.

Repeated cultures of the genital and oral ulcers were negative for herpes simplex virus. The rapid plasma reagin and the fluorescent treponemal antibody tests were negative on two occasions. Gram-stained smears of the genital ulcer did not contain organisms suggestive of *Haemophilus ducreyi*. Two separate samples of serum contained antibodies to HIV, as determined by enzyme-linked immunosorbent assay and confirmed by Western blot. The CD4 cell count was 195 cells/mm^3 and the CD8 cell count was 1746/mm^3. There was no reaction to the intradermal injection of trichophyton or mumps antigens. Results of computed tomographic examination of the pelvis were normal. Microscopic examination of biopsy specimens from the vestibular ulcer disclosed acute and chronic inflammation, ulceration, granulation tissue, moderate dysplasia, and condylomatous changes. Cultures for acid-fast bacilli, actinomyces, and nocardia were negative. Cultures for HIV were not done.

The ulcer failed to respond to treatment with oral amoxicillin–clavulanic acid. Fever and a rash developed when the patient was given oral metronidazole and trimethoprim-sulfamethoxazole. In June 1987 treatment was begun with zidovudine 900 mg/day. One month later the dose was reduced to 600 mg/day. In association with zidovudine treatment the vestibular ulcer gradually reepithelialized (Fig. 2) and the genital warts partially resolved. No new oral aphthae or genital ulcers appeared.

Comment

We were unable to define an etiologic agent for the intractable genital ulcer in this HIV-infected woman. Our inability to find any evidence of syphilis, chancroid, herpes simplex virus infection, or other causes of genital ulcer disease, the failure of the lesion to respond to treatment directed at these established causes of genital ulceration, the nonspecific nature of the biopsy findings, and the healing of the ulcer in association with zidovudine administration all suggest that the ulcer may have been a manifestation of HIV disease.

As of March 31, 1990, 128,319 cases of HIV disease in the United States and its territories had been reported to the Centers for Disease Control.[1] It has been estimated that between 1 and 2 million Americans have already been infected with HIV.[2] Although the natural history of HIV infection is incompletely understood at present, it can be expected that unusual presentations of HIV disease will increase. Health care professionals must be aware of the ever-broadening spectrum of the disease.

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Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding

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Endometrial sampling is the mainstay of management of the postmenopausal patient with uterine bleeding. Thirty women with postmenopausal bleeding were studied prospectively. Before endometrial sampling, a vaginal probe ultrasonographic examination was performed. Eleven patients demonstrated a thin "pencil line" endometrial echo in which the maximum anteroposterior thickness on the long axis view was ≤5 mm. All eleven patients had minimal tissue obtained on biopsy and a pathology report of "tissue insufficient for diagnosis." Seventeen patients had an echogenic endometrium ≥6 mm. Pathology reports of their samples revealed tissue insufficient for diagnosis (two cases), proliferative endometrium (six), secretory endometrium (three), hyperplastic endometrium (three), polyp (two), and endometrial cancer (one case). Two additional patients had no endometrial echo visualized because of associated myomas. These findings suggest (1) that the absence of significant endometrial tissue (echo ≤5 mm) on vaginal ultrasonography in cases with postmenopausal bleeding is uniformly associated with tissue insufficient for diagnosis, and (2) when endometrial thickness is ≥6 mm the histologic diagnosis should be determined in the pathology laboratory. (Am J Obstet Gynecol 1990;163:119-23.)

Key words: Postmenopausal bleeding, histopathology, ultrasonography, vaginal probe ultrasonography

Endometrial cancer is the most common gynecologic malignancy yet also the one with the best survival statistics. Approximately 80% of endometrial cancer occurs in postmenopausal women. Because these patients usually are seen because of vaginal bleeding, it has been dogma in gynecology that the endometrium of postmenopausal women must be sampled. When the postmenopausal woman is taking hormone replacement therapy, such a rule should be modified. Much of the current clinical approach to such patients stems from the landmark paper of Padwick et al.[1] in 1986. They studied 102 women who were continuously receiving estrogen therapy and 12 days of progestin per month. They then correlated the day of onset of bleeding with the endometrial histology obtained by endometrial biopsy. In all cases, regardless of the dose or type of estrogen and progestin used, inappropriate histopathologic types (predominantly proliferative or hyperplastic endometrium) were always associated with bleeding before day 10 of the addition of the progestin. Secretory or absent endometrial tissue (the expected pathologic findings) was always associated with bleeding on day 11 or after. With the recently revealed benefits of hormone replacement therapy, the number of patients receiving therapy has increased.[2] Thus the total number of patients with inappropriate postmenopausal bleeding will also increase.

New vaginal probe ultrasonographic transducers are of higher frequency and closer proximity to structures being studied. This results in excellent near-field resolution, despite high degrees of magnification, thus yielding a type of "sonomicroscopy."[3] Previously investigators used high-resolution abdominal ultrasonographic equipment to assess uterine content.[4] We undertook this study to determine whether vaginal probe ultrasonography could demonstrate endometrial content in patients with abnormal postmenopausal bleeding and to correlate the vaginal ultrasonographic findings with the pathology of the tissue obtained by endometrial sampling.

Material and methods

This was a prospective pilot study. Thirty postmenopausal women with abnormal uterine bleeding were scheduled for outpatient suction endometrial sampling. Just before sampling a vaginal probe ultrasonographic examination was performed with either a 7.5 MHz Siemens Sonoline system, Iselin, N.J., or a 5.0 MHz Aloka 633 system, Tokyo. The uterus was scanned in long-axis and coronal views with special emphasis on the endometrium. The scanning of the uterus was first sagittal planes in an attempt to "section" the uterus from side to side to determine regularity of the endome-

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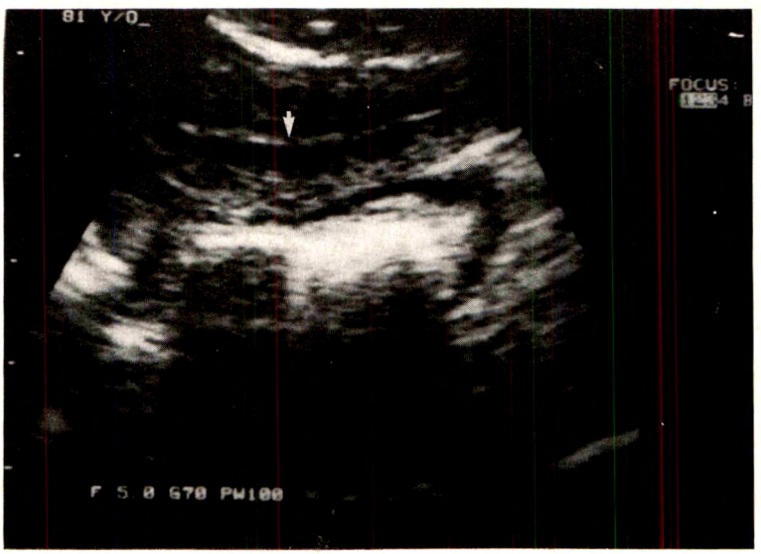


Fig. 1. Long-axis vaginal ultrasonographic views of an 81-year-old patient who had postmenopausal bleeding. The endometrial echo appears as a thin "pencil line" (1 mm) linear echogenicity *(white arrow)*. Notice the hypoechoic "halo" surrounding it. Endometrial sampling revealed tissue insufficient for diagnosis.

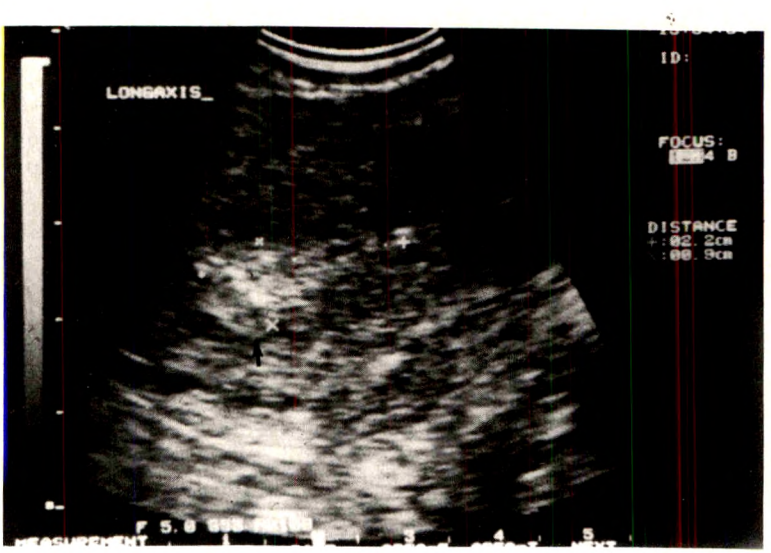


Fig. 2. View of a 55-year-old postmenopausal patient receiving hormone replacement therapy who consistently bled on or before day 6 of progestin. Anteroposterior thickness of the endometrium on this long-axis view was 9 mm *(black arrows)*. The pathology report on endometrial sampling revealed proliferative endometrium.

trium. The same maneuver was performed in a coronal plane. Anteroposterior measurements of endometrial thickness were taken from long-axis views to avoid oblique semicoronal views that might cause the endometrium to appear thicker. The entire pelvis was additionally examined to rule out any other gynecologic pathogic condition. Suction aspiration was then performed with a 3 mm stainless steel cannula (Vabra, Berkeley, Calif.). Care was taken to attempt to sample all areas of the endometrial cavity; tissue obtained was sent to the laboratory for pathologic examination.

Results

Thirty women (age range, 39 to 81 years) were studied. Twelve women had postmenopausal bleeding and were not receiving hormonal replacement therapy. The remaining 18 received estrogen/progestin replacement but had bled at inappropriate times according to the schemata of Padwick et al.[1] Ultrasonographic findings

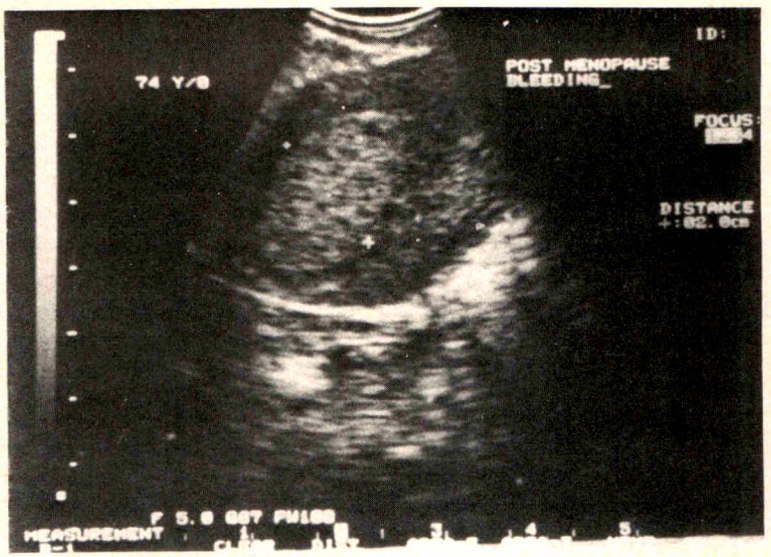


Fig. 3. A 74-year-old postmenopausal patient who was not receiving hormonal therapy presented with a history of postmenopausal bleeding. The long-axis vaginal ultrasonographic view here demonstrates anteroposterior thickness of endometrium of 2.0 cm *(between calipers)*. The pathology report on tissue obtained at endometrial sampling was glandular hyperplasia.

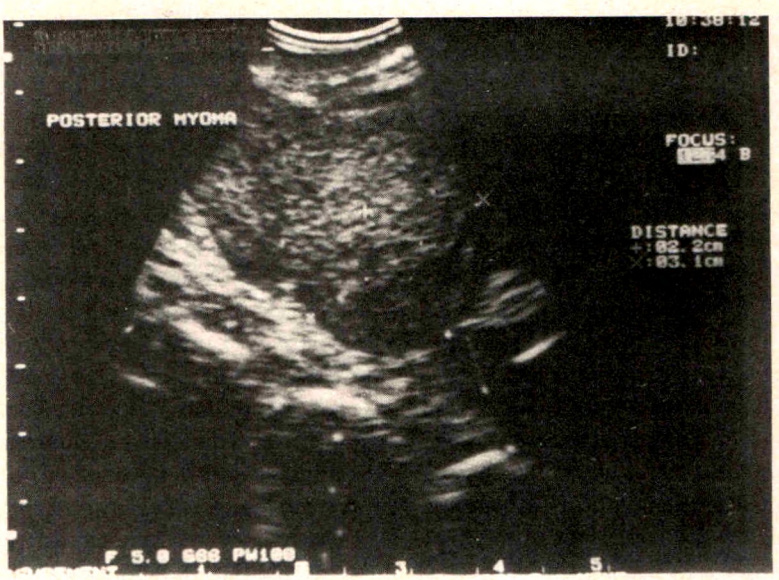


Fig. 4. A 59-year-old patient had postmenopausal bleeding. Bimanual examination revealed a normal-sized (upper limit), irregular uterus. A vaginal ultrasonographic view revealed a posterior myoma (3.1 × 2.2 cm). No endometrial echo could be identified. Endometrial sampling revealed proliferative endometrium with small foci of glandular hyperplasia.

revealed a thin "pencil line" linear endometrial echogenicity of 5 mm thickness total anteroposterior diameter in 11 patients (range, 1 to 5 mm). This was measured in the long-axis view (Fig. 1). Seventeen patients had an echogenic endometrium, measuring 6 mm, (range, 6 to 25 mm) (Figs. 2 and 3). In two patients endometrial echo could not be identified because of multiple myomas (Fig. 4). Pathology specimens in all 11 patients with endometrial thickness ≤5 mm was reported as "tissue insufficient for diagnosis" or "scant cellular material." In the 17 patients with endometrial thickness ≥6 mm, the pathology revealed proliferative endometrium (six cases), secretory endometrium (three), hyperplastic endometrium (three), polyp (two), tissue insufficient for diagnosis (two, and endometrial cancer (one). In the two additional patients

with no endometrial echo because of multiple myomas, one had tissue insufficient for diagnosis and the other showed proliferative endometrium with small foci of glandular hyperplasia, respectively.

Comment

It would appear from this preliminary study that endometrial thickness ≤5 mm maximum anteroposterior diameter measured on a long-axis view by vaginal probe ultrasonography is uniformly associated with minimal tissue obtained by sampling. In menopause the normal endometrium becomes thin and atrophic as a result of a lack of epithelial stimulation. The atrophic mucosa is prone to superficial punctate ulceration. This can result in "senile endometritis" and probably represents the cause of the bleeding when there is scant tissue present.[5]

It also appears from this study that when the endometrial thickness is ≥6 mm, a variety of pathologic diagnoses can be encountered. In such instances the histologic diagnosis therefore is made in the pathology laboratory, and not by ultrasonographic examination. When myomas preclude endometrial visualization, endometrial sampling remains mandatory.

A discrepancy may exist when significant endometrial tissue is present ultrasonographically (endometrial echo ≥6 mm) and the sampling reveals a diagnosis of tissue insufficient for diagnosis. This may cause great concern on the part of the clinician. In the past, whenever a diagnosis of tissue insufficient for diagnosis was encountered in the clinical context of postmenopausal bleeding, the question arose whether the operator had missed tissue because the endometrial cavity was not entered. In our study we had two patients in the group with endometrial echo ≥6 mm whose pathology report revealed tissue insufficient for diagnosis. Both patients had an endometrial echo measuring 6 mm. We used 5 mm as a cutoff point because although two patients with a 6 mm endometrial echo had tissue insufficient for diagnosis, there were several patients with 6 mm endometrial echoes who also exhibited proliferative endometrium.

The data from patients in this study who had a history of postmenopausal bleeding cannot be extrapolated to draw conclusions about mass screening of asymptomatic postmenopausal women. Further study is required to determine if an echogenic endometrium (≥6 mm) should be considered an indication for sampling in a nonbleeding patient. Thirty-five percent (5/17) of our patients who had bleeding and endometrial echos ≥6 mm had no significant pathologic findings (tissue insufficient for diagnosis or secretory endometrium). We also recognize that there are limitations of vaginal ultrasonography in the postmenopausal patient. It can be technically difficult to perform if the introitus has become stenotic. Coexisting myomas can obscure the visualization of the endometrial echo. We believe that measurements of the endometrial thickness should be made from the long-axis view. Such anteroposterior diameters are more reliable because the coronal plane, when obtained with vaginal probe ultrasonography, can actually be cut somewhat obliquely and reveal falsely elevated measurements.

Another possible shortcoming of our study was the fact that all patients had office sampling procedures, not formal curettage. There is the possible concern that such sampling procedures may be slightly less reliable than traditional fractional curettage.

There was only one malignancy in our series. This was an exophytic polypoid lesion that on vaginal probe ultrasonography did not suggest myometrial invasion. In most patients (Fig. 1) we observed the subendometrial halo of anechoic tissue described by Fleischer et al.,[4] but this was not a consistent finding. In no case was such a layer disrupted, but as mentioned previously there were no invasive lesions.

Six of the 17 positive scans produced pathologic tissue (hyperplasia, polyp, and cancer) for a positive predictive value of 35%, whereas none of the negative scans did (negative predictive value, 100%). This is similar to the experience in ovarian screening—a very sensitive but not very specific technique. We would submit, however, that proliferative endometria, although not conventionally thought of as "pathologic," are certainly not normal in a postmenopausal group regardless of the use of hormone replacement therapy.

Other important issues are raised by this work and should be considered in any further studies. We did not have the ability to follow up these patients longitudinally to determine the endometrial changes throughout the month with the administration of progestins, or precisely how the addition of steroids affects the density and thickness of postmenopausal endometria. Finally, the question of whether there would be ultrasonic resolution of proliferation with appropriate progestin therapy should be addressed.

This was a pilot study; obviously many more patients are required to confirm and extend these results. In this study 37% of patients (11/30) had thin "pencil line" endometrial echoes (≤5 mm in diameter). All 11 had tissue insufficient for diagnosis. If further study shows that such ultrasonographic findings are uniformly associated with a lack of significant endometrial tissue, then perhaps a large number of women could be reliably spared endometrial sampling and therefore avoid the risk, discomfort, and expense of the procedure. We also think that further studies with larger numbers of women, including those without a known history of vaginal bleeding and those not receiving hormone replacement therapy, must precede attempts to extrap-

olate the data to a screening situation. If these studies confirm our data, the use of endovaginal ultrasonography as a screening procedure before endometrial sampling should be considered.

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Transabdominal and transvaginal ultrasonography in the diagnosis of ectopic pregnancy: A comparative study

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Thirty-four patients believed to have ectopic pregnancies were examined by transabdominal and transvaginal ultrasonography. Twenty-five patients had tubal pregnancy confirmed operatively within 24 hours after ultrasonographic examination. In these cases adnexal findings highly suspicious for ectopic pregnancy were found in 68% of cases by transabdominal ultrasonography and in 84% by transvaginal ultrasonography. A distinct adnexal gestational sac was apparent in 32% of cases by transabdominal ultrasonography and in 64% of cases by transvaginal ultrasonography. Transvaginal ultrasonography was significantly more accurate ($p < 0.01$) in identifying an adnexal gestational sac and allows more detailed adnexal imaging. (AM J OBSTET GYNECOL 1990;163:123-8.)

Key words: Ectopic pregnancy, transvaginal ultrasonography, adnexal mass

Recent literature[1-3] has reported an increase in the incidence of ectopic pregnancies. The development of high-resolution ultrasonography and sensitive pregnancy tests has made it possible to diagnose ectopic pregnancy at an earlier stage of development than has previously been possible.

Transvaginal ultrasonography has been reported to be accurate in the evaluation of adnexal abnormalities[4,5] and ectopic pregnancies.[6,7] The diagnosis of tubal pregnancy by inclusion is sensible today, with the reported increase in both ectopic pregnancy and concomitant ectopic and intrauterine gestations.[8-10]

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Recent reports in the literature have compared the ability of transabdominal ultrasonography and transvaginal ultrasonography to detect ectopic pregnancy.[11-17] These studies report findings in a heterogeneous population of patients with both normal and pathologic gestations. The purpose of this study was to prospectively compare the diagnostic accuracy of these two modalities in a pure population of operatively confirmed cases of ectopic pregnancy.

Material and methods

Thirty-four of all patients with suspected ectopic pregnancy, who were referred to the Perinatal Laboratory at Barnes Hospital from Jan. 1, 1988 to Jan. 4, 1989, were evaluated ultrasonographically both transabdominally and transvaginally. All these patients had a high index of suspicion for ectopic pregnancy on the basis of history of a previous ectopic gestation, prior tubal factor infertility, or previous tubal surgery. All of the patients had abdominal pain and/or vaginal bleed-

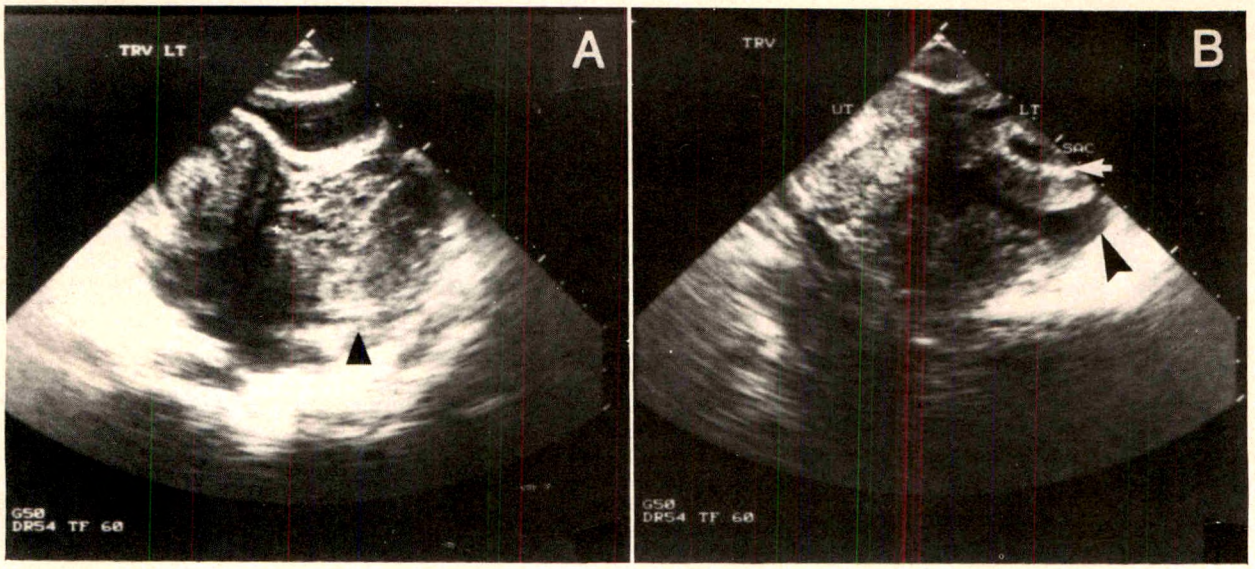


Fig. 1. A, Transabdominal transverse scan with a large, complex left adnexal mass *(black arrow)*. **B,** Transvaginal transverse scan of the same patient revealing a left adnexal gestational sac *(white arrow)* lying beneath the left ovary *(LT)*. Fluid is represented by *black arrow*.

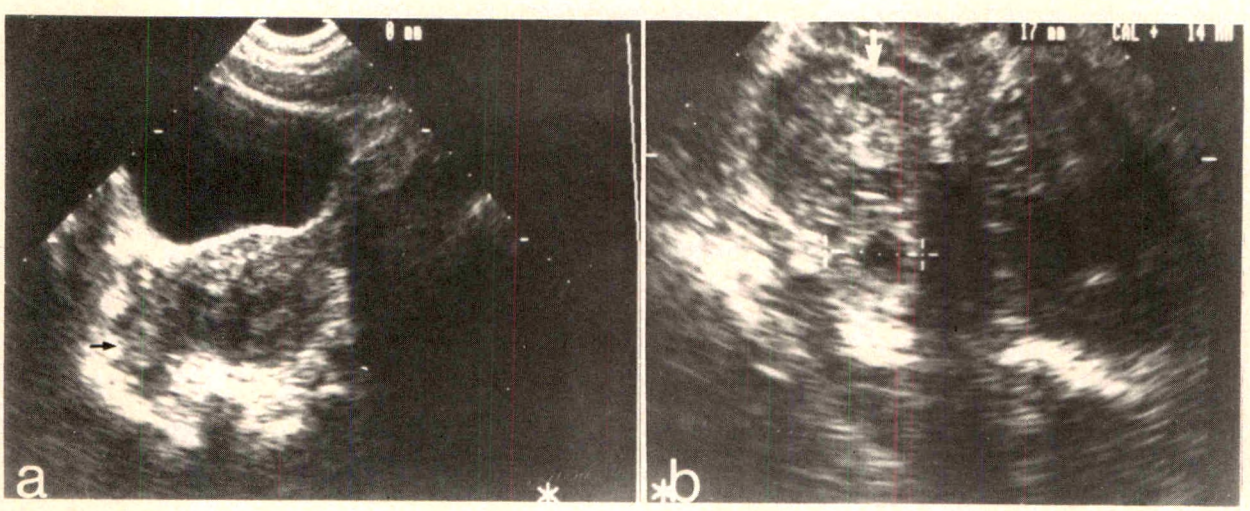


Fig. 2. a, Transabdominal transverse scan with an irregular right adnexal mass with echogenic focus posteriorly *(small black arrow)*. **b,** Expanded transverse scan of the same patient revealing an empty sac in the right adnexa *(electronic calipers)*. The right ovary *(white arrow)* is seen superiorly.

ing when first seen and were found to have a qualitatively positive urine or serum human chorionic gonadotropin (hCG) test result. All of the patients lacked an intrauterine gestational sac at the time of sonographic evaluation. In 9 cases the diagnosis of ectopic pregnancy was excluded on the basis of the lack of adnexal findings on ultrasonographic evaluation and at laparoscopy and/or the pathologic demonstration of villi at endometrial curettage. Laparoscopic examination was done in 6 of these 9 cases. One of those and the seventh patient had villi on endometrial curettage. Two others had only follow-up in their doctors' offices.

Twenty-five patients had a tubal pregnancy confirmed operatively and formed the subgroup of the study population that was operated on. These patients were first seen at 4 to 12 weeks of amenorrhea (mean 8.2 weeks) at the time of evaluation. The mean age of the patients was 28.5 years (range 18 to 39). Gravidity ranged from 0 to 8 (mean = 3) and parity was low (mean = 1), reflecting a large number of patients with

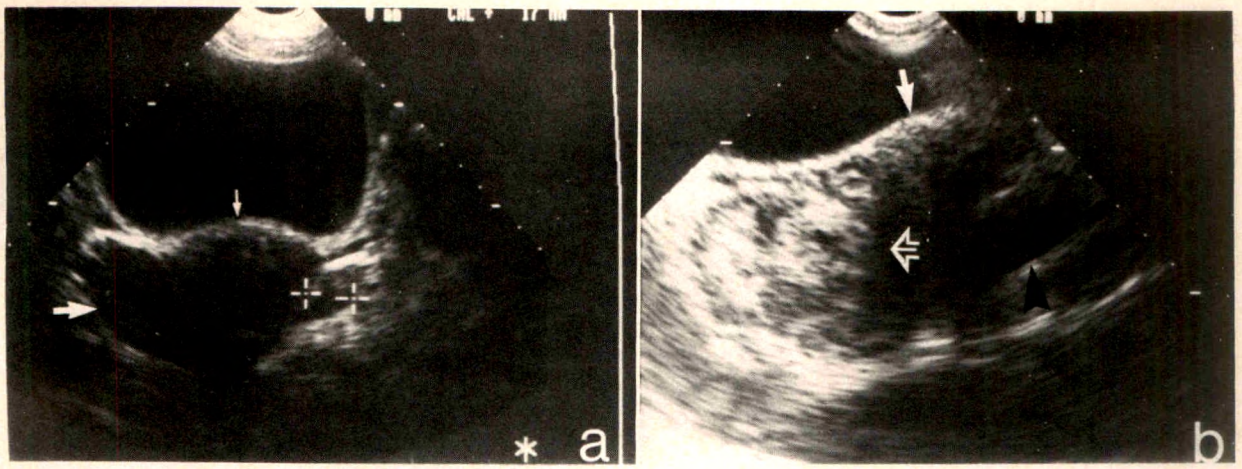


Fig. 3. a, Transabdominal transverse scan with a complex, noncystic right adnexal mass *(thick arrow)* lying immediately adjacent to the uterus *(thin arrow)*. The left ovary is marked by *electronic calipers*. **b,** Transvaginal transverse scan of the same patient showing a normal right ovary *(white arrow)*. A separate, complex right adnexal mass containing a gestational sac also can be identified *(open arrow)*. Fluid is represented by *black arrow*.

infertility. All ultrasonographic examinations were performed by experienced sonographers and verified by a physician. Real-time scans were performed with an ATL UltraMark 4, with a 3.5 or 5.0 MHz abdominal sector transducer and a 5.0 MHz vaginal probe, or a Hitachi EUB-450, with a 3.5 MHz abdominal convex transducer and a 6.5 MHz vaginal probe. All patients were scanned initially with a standard transabdominal technique that included a full urinary bladder and systematic evaluation of the uterus, adnexal areas, and cul-de-sac. After this, the bladder was emptied and systematic transvaginal sonographic reevaluation of the pelvis was carried out.

The adnexal findings were described as (1) a gestational sac containing a fetal pole with or without heart motion, (2) an empty saclike structure surrounded by a thick rind of echoes, or (3) a complex or solid mass separate from a recognizable ovary (Figs. 1 to 3). All 25 of these patients underwent operation for confirmation of the sonographic findings within 24 hours of evaluation.

Results

In all 34 cases the uterus had no sonographic evidence of a gestational sac but pregnancy test result was positive. An endometrial cast of variable size (from 4 to 15 mm) was a common intrauterine finding in 25 cases of ectopic gestation. In 10 cases it was larger than 10 mm. In two cases (8%) intrauterine fluid collections were detected by both transabdominal ultrasonography and transvaginal ultrasonography. These were easily distinguished from a true gestational sac, however, by the absence of a double decidual sac sign.

Adnexal findings, which were highly suspicious for ectopic pregnancy in 25 operated cases, were shown in 17 patients (68%) with transabdominal ultrasonography and in 21 patients (84%) with transvaginal ultrasonography. This difference is not statistically significant, $p > 0.05$ (Table I). In the 17 patients with adnexal findings on transabdominal ultrasonography, 9 cases (36%) showed evidence of an adnexal mass separate from the ovary. Six (24%) of these masses were complex cysts and 3 (12%) were solid masses. A distinct adnexal gestational ring was apparent in only 8 cases (32%) with transabdominal ultrasonography. In the 21 patients with positive adnexal findings on transvaginal ultrasonography, a gestational ring was clearly demonstrable in 16 of the scans (64%). This difference is statistically significant, $p < 0.01$ (Table I). All of the 5 remaining patients (20%) were noted to have a complex or cystlike adnexal mass separate from the ovary. In all cases the sonographically positive adnexal findings were shown to be the site of the ectopic gestation at operation. The adnexal findings in all 34 cases are presented in Table II.

Table I. Comparison of adnexal findings on transabdominal and transvaginal ultrasonography

Finding	*Abdominal*	*Vaginal*
Gestational sac	8 (32%)*	16 (84%)*
Mass	17 (68%)†	21 (84%)†

*$p < 0.01$.
†p = NS.

There was only one case in which an adnexal mass was identified by transabdominal ultrasonography and not by transvaginal ultrasonography. In this case at op-

Table II. Adnexel findings of 34 patients with suspected ectopic pregnancy

Finding	*Ectopic pregnancies (operated on) (n = 25)*		*Nonectopic pregnancies (n = 9)*	
	TAU	*TVU*	*TAU*	*TVU*
Sac	8	16	—	—
Complex mass	6	4	2	2
Solid mass	3	—	—	—
Cyst	—	1	2	4
TOTAL	17	21	4	6

TAU, Transabdominal ultrasonography; *TVU*, transvaginal ultrasonography.

Table III. Intraabdominal bleeding

Transvaginal ultrasonography (ml)	*Estimation at operation (ml)*
35	150
90	150
25	300
26	75
0	100
10	75
14	250
0	<100
0	Small
0	50
0	Minimal
8	Small
13	Small
0	50
13	<100
0	<100
0	50-100
26	200
11	75

eration the tube was found to be adherent to the uterine fundus, omentum, and anterior abdominal wall and thus held out of the field of visualization by the transvaginal probe. The gestational sac was found to be separated from the ovary by transvaginal ultrasonography in 17 cases and by transabdominal ultrasonography in 7 cases.

When all 34 patients were screened by transabdominal ultrasonography and the sac or a mass separated from ovary was shown, sensitivity was 44%, specificity 100%, and positive and negative predictive values were 100% and 30%. By transvaginal ultrasonography the respective values were 72%, 100%, 100%, and 56%.

At the time of operation 20 (80%) of the patients had an intraoperative estimate of the amount of free blood or fluid in the cul-de-sac. In 19 of these cases we were able to measure the fluid from pictures (Table III). In the cases in which a small amount of blood was found at operation, transvaginal ultrasonography revealed either no demonstrable free fluid or a calculated amount <26 ml. Free fluid was observed in 12 patients (54%) by transabdominal ultrasonography and in 14 patients (64%) by transvaginal ultrasonography. The estimated amount of intraabdominal blood present at the time of operation ranged from 50 to 1500 ml over the entire study population.

Laparotomy was performed in 24 cases. The tube was unruptured in 86% of the patients, allowing conservative surgery for tubal salvage to be carried out. In the remaining case nonsurgical conservative management was used because of minimal sonographic findings and few symptoms. The decision was made to monitor the patient's serial quantitative serum hCG values, which fell to negative levels. The adnexal gestational sac was seen in 75% of unruptured cases by transvaginal ultrasonography.

Comment

All the patients in the study had a high index of suspicion for the presence of an ectopic pregnancy on the basis of past reproductive or gynecologic history, clinical presentation, and the presence of a positive qualitative pregnancy test result on either blood or urine. It has been reported that transabdominal sonographic visualization of a normal intrauterine pregnancy should be possible at first international standard β-subunit hCG levels in excess of 6500 mIU/ml.[18] Transvaginal visualization of an intrauterine gestational sac is possible at first international standard β-subunit hCG values >1800 mIU/ml[19] and at intact hCG levels >1000 mIU/ml on enzyme-linked immunosorbent assay.[20] Quantitative hCG levels were not known at the time of sonographic evaluation in our study population of 25 ectopic pregnancies. Because surgical evaluation was carried out within 24 hours after patients were first seen, quantitative hCG values, if determined at all, were only available in 11 cases in retrospect (range 139 to 6000 mIU/ml; mean 2176 mIU/ml). Because ectopic gestation represents an abnormal gestational state in which hCG levels frequently do not follow the normal incremental doubling pattern of an intrauterine pregnancy, the use of an isolated quantitative hCG level as a diagnostic tool in the ectopic

gestation may be limited. This may be particularly true of situations in which the length of amenorrhea is not known exactly and the quantitative hCG is at a subthreshold value. High-resolution transvaginal ultrasonography appears to be a powerful tool in the evaluation of suspected ectopic gestations because of its ability to demonstrate an intrauterine gestational sac very early in the course of gestation.[21, 22]

Nonovarian adnexal masses were visualized by transabdominal ultrasonography in 68% of cases and by transvaginal ultrasonography in 84% of cases in our population, demonstrating the improved efficacy of transvaginal ultrasonography over transabdominal ultrasonography. This improvement was more evident in the ability of transvaginal ultrasonography to visualize an adnexal gestational sac (64%) when compared with transabdominal ultrasonography (32%), $p < 0.01$. These results compare favorably with other reports in the literature.[11-17] The additive effect of using both imaging modalities is underscored in the single case where an ectopic mass was fixed by adhesions and could be visualized only by the abdominal scans. It is important to keep in mind that the high-resolution transvaginal transducers are limited in their imaging ability to structures that lie in the true pelvis and within their shorter focal zone. Thus it is prudent generally to use transabdominal ultrasonography to image the pelvis and document normal and abnormal anatomy and then use transvaginal ultrasonography for further detail of the pelvis with particular attention to any abnormal findings.

The presence of noncystic adnexal masses in cases of suspected ectopic gestation have been reported to have a higher positive predictive value than do cystic adnexal masses.[6] In our series the complex cystic mass was the more common finding. This may be explained by the fact that transvaginal ultrasonography allows a more detailed view of the true architecture of masses that appear solid on transabdominal ultrasonography.

Fluid was found in 54% of cases by transabdominal ultrasonography and in 64% by transvaginal ultrasonography. The ultrasonography was negative in most cases if there was <100 ml of blood in the pelvis at operation. Although 100 ml of blood should be readily visualized with transvaginal ultrasonography, the time from ultrasonography to surgical evaluation was typically several hours, and thus slow or early bleeding could have occurred during this interval.

Of greatest clinical significance is the fact that 86% of the patients had unruptured ectopic pregnancies that were amenable to treatment by salpingotomy, thereby saving the tube for future reproductive effort. High-resolution transvaginal ultrasonography appears to have much to offer in facilitation of the recognition of both intrauterine and ectopic gestational sacs. Earlier diagnosis of ectopic pregnancy enables the practitioner to achieve tubal salvage more frequently and allows the patient to escape the added morbidity of major intraabdominal bleeding.

In summary, transvaginal ultrasonography has added a new dimension to the early evaluation and diagnosis of ectopic pregnancy with enhanced ability to localize and identify an ectopic gestational sac, provide further architectural detail in the case of a complex adnexal mass, and allow more sensitive detection of small amounts of free fluid in the cul-de-sac. The clinical benefit to the patient is the greater opportunity of the physician to attempt and achieve tubal salvage. Because of the probability of distortion of normal pelvic anatomy in patients at risk for ectopic pregnancy, the additive value of systematic transabdominal and transvaginal scanning should not be ignored.

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Niemann-Pick disease associated with nonimmune hydrops fetalis

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The number of metabolic disorders associated with nonimmune hydrops fetalis is very small and includes only Gaucher disease, GM_1 gangliosidosis type 1, Hurler syndrome, and mucolipidosis type I. We report another association of a nonimmune hydrops fetalis with Niemann-Pick disease as evident by electron microscopy, and wish to add this disorder to the list of conditions associated with nonimmune hydrops fetalis. (Am J Obstet Gynecol 1990;163:128-9.)

Key words: Nonimmune hydrops fetalis, Niemann-Pick disease

Nonimmune hydrops fetalis is a condition that affects non-Rh sensitized pregnancies, characterized by excessive fluid accumulation within fetal extravascular compartments and body cavities. The causes of nonimmune hydrops fetalis are numerous. In about 40% of fetuses, nonimmune hydrops fetalis is an idiopathic condition and no cause can be elicited.[1] Conditions associated with nonimmune hydrops fetalis include hematologic, pulmonary, neurologic, gastrointestinal, hepatic, genitourinary, infectious, neoplastic, cardiovascular, vascular, skeletal, chromosomal, and metabolic disorders.

The metabolic derangements associated with nonimmune hydrops fetalis are drawn from a number of pathways that involve either synthesis or storage disorders. The mechanisms for the development of hydrops in cases of storage disease may involve visceromegaly and obstruction of venous return.[2] The storage diseases that have been reported include Gaucher disease, GM_1 gangliosidosis type 1, Hurler syndrome (mucopolysaccharidosis I) and mucolipidosis I (sialidosis).

We recently encountered a fetus with nonimmune hydrops fetalis in which the cause could be attributed to another metabolic disorder not described in the English literature. The sonographic evidence of nonimmune hydrops fetalis was first documented at 19 weeks' gestation and included severe ascites and bilateral hydrothorax. The fetal liver appeared large and occupied most of the fetal abdomen. The patient refused pregnancy termination and did not agree to undergo either amniocentesis or percutaneous umbilical blood sampling. Repeated sonograms obtained at 25 and 30 weeks' gestation revealed worsening of the ascites and hydrothorax with appearance of marked skin edema (8 mm). Polyhydramnios was evident in all scans.

In utero fetal death was noted at 36 weeks' gestation. One day later the patient spontaneously went into labor and a severely hydropic neonate was vaginally delivered.

At autopsy a 1620 gm male infant with hydrops was

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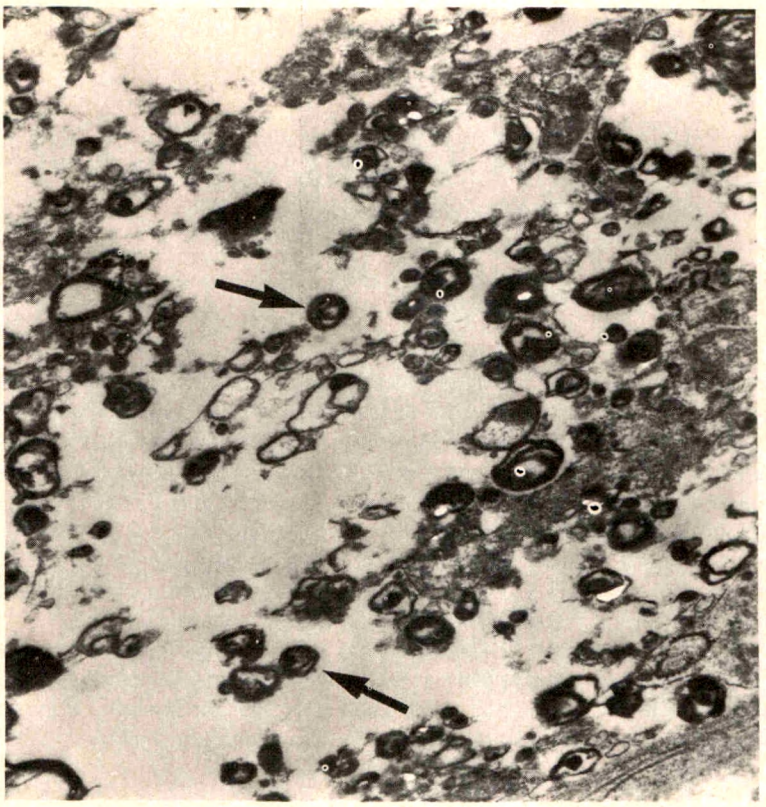


Fig. 1. Electron microscopic picture of cytoplasm of foamy cell from spleen shows many electron dense concentric lamellae *(arrows)*, granules, and tubular structures. (Original magnification × 20,000.)

noted. There were severe ascites, a hydrothorax, and generalized edema. The liver and spleen were greatly enlarged, filling the abdomen.

Microscopic examination showed 30% replacement of the liver and 80% replacement of the spleen by "foamy" histiocytes. Occasional "foamy" histiocytes were present in the marrow. There was also involvement of the neurons of the brain and spinal cord.

By electron microscopy (Fig. 1) numerous cytoplasmic inclusions were seen in "foamy" histiocytes in the liver and spleen. The inclusions were round or oval, small, and in groups. Some were discrete myelin-like figures that consisted of concentric osmiophilic lamellae or appeared as crystalline granules of lipid or as tubular structures, typical of Niemann-Pick disease.

Niemann-Pick disease is characterized by the accumulation of sphingomyelin in the reticuloendothelial cells of the liver, spleen, bone marrow, and lymph nodes. About 85% of the patients have the classic disease characterized by hepatosplenomegaly and intellectual deterioration that becomes manifest during the first year after birth, leading to death within 1 or 2 years. This disease has not been reported as a cause of nonimmune hydrops fetalis and therefore should be included in the list of metabolic conditions associated with this entity.

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Risk factors for preterm premature rupture of fetal membranes: A multicenter case-control study

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To assess the association between women with preterm premature rupture of membranes and 41 potential risk factors, we conducted a case-control study in six United States tertiary perinatal centers. The study involved completion of a comprehensive questionnaire for 341 women with preterm premature rupture of membranes in singleton pregnancies from 20 to 36 weeks' gestation and 253 control women matched for maternal age, gestational age, parity, clinic or private patient status, and previous vaginal or cesarean delivery. Univariate analysis revealed 11 variables associated with a significantly ($p < 0.05$) increased risk of preterm premature rupture of membranes. After multiple logistic regression analysis, three variables remained in the model as independent risk factors: antepartum vaginal bleeding in more than one trimester (odds ratio 7.4; 95% confidence interval, 2.2, 25.6), current cigarette smoking (odds ratio, 2.1; 95% confidence interval, 1.4, 3.1), and previous preterm delivery (odds ratio, 2.5; 95% confidence interval, 1.4, 2.5). Cessation of cigarette smoking by pregnant women may reduce the risk of preterm premature rupture of membranes. Further study is necessary to determine the nature of the relationship between antepartum vaginal bleeding and preterm premature rupture of membranes. (Am J Obstet Gynecol 1990;163: 130-7.)

Key words: Premature rupture of membranes, cigarette smoking, preterm delivery

Premature birth remains the most frequent cause of perinatal morbidity and mortality in North America and Europe, and preterm premature rupture of the fetal membranes occurs in a significant proportion (15% to 40%) of preterm births.[1] The causes of preterm or low-birth-weight deliveries have been scrutinized and investigated intensively, but the majority of preterm births occur without an established cause. Several epidemiologic factors have been correlated with preterm labor but have been studied in surprisingly few reports.

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Seven previously published studies have suggested various risk factors for preterm premature rupture of membranes.[2-8] These studies, however, were too small, uncontrolled, dated, or not specifically focused on risk factors for preterm premature rupture of membranes. For example, vaginal bleeding in any trimester and a history of preterm labor have been linked with the occurrence of preterm premature rupture of membranes. In an Australian study, vaginal bleeding during at least one trimester of pregnancy had occurred in 18 (30%) of 60 women with preterm premature rupture of membranes at 26 to 37 weeks' gestation.[2] A history of preterm delivery was found in the prior pregnancy of nine (20.5%) of the 44 multigravid women with preterm premature rupture of membranes. However, no control subjects were included in this study.

Cigarette smoking or a history of gynecologic surgery also have been implicated in preterm premature rupture of membranes. In a Swedish study of 3391 deliveries, 30 women with preterm premature rupture of membranes were compared with 30 control subjects matched for age, parity, duration of pregnancy, and socioeconomic status (all were middle class).[3] In this study bleeding in the first or third trimester ($p < 0.01$), smoking more than 10 cigarettes per day ($p < 0.01$), and previous gynecologic surgery ($p < 0.01$) were

found to be associated with an increased risk of preterm premature rupture of membranes. Four of the 30 cases of preterm premature rupture of membranes were twin gestations, whereas all of the controls were singleton pregnancies. In addition, a nonsignificant trend toward an excess number of prior therapeutic abortions was found in cases of preterm premature rupture of membranes compared with control subjects in this study. This trend agreed with the results of Koller and Eikhorn[4] who reported an increased risk of preterm premature rupture of membranes in women whose first pregnancy was voluntarily terminated by suction curettage ($p < 0.001$).

An analysis of data from the United States Collaborative Perinatal Project from 1958 through 1966 reported a statistically significant association between preterm premature rupture of membranes and prior surgery of the cervix, coitus at least weekly in the month before delivery, and histologic evidence of chorioamnionitis.[5] Cigarette smoking was associated with premature rupture of membranes at term but not with preterm premature rupture of membranes. Paradoxically, women who smoked 20 or more cigarettes per day had a slightly lower risk of premature rupture of membranes (6%) than those who reported smoking <20 cigarettes per day (7%). A significant association between cigarette smoking and preterm premature rupture of membranes and an association between cigarette smoking and abruptio placentae and placenta previa were reported by Meyer and Tonascia.[6] Others, however, found no such association between cigarette smoking and preterm premature rupture of membranes or abruptio placentae in a survey of 4440 women of varied socioeconomic status who were delivered in 1960 and 1961 in Charleston, South Carolina.[7]

Preterm premature rupture of membranes had also been linked in previous studies with indicators of intrauterine infection, such as the presence of *Bacteroides* species and histologic evidence of chorioamnionitis. *Bacteroides fragilis* organisms were isolated from the cervix, placenta, or amniotic fluid of 23% of women with preterm premature rupture of membranes but none of the controls.[8] Similarly, in a study of a predominantly black, lower socioeconomic status population in Brooklyn, a statistically significant association occurred between preterm premature rupture of membranes and the isolation of *Bacteroides* species in vaginal cultures ($p < 0.03$).[8]

We therefore undertook a prospective, multicenter, case-control study of preterm premature rupture of membranes. We used a comprehensive questionnaire among women in six tertiary perinatal centers in the United States to obtain detailed information about the risk factors for preterm premature rupture of membranes. This information will be used in the development of strategies for the prevention of preterm premature rupture of membranes and in the design of further studies about its cause, pathogenesis, and clinical management.

Methods

Study subjects. From 1982 to 1983 a multicentered case-control study was conducted by collaborating institutions including Brigham and Women's Hospital in Boston, Abbott-Northwestern Hospital in Minneapolis, University of Pittsburgh Magee-Womens Hospital, University of Texas Health Science Center Hospital in San Antonio, University of Washington Hospital in Seattle, and Medical Center Hospital of Vermont in Burlington. The Central Data Coordinating Center was located at The Johns Hopkins University School of Hygiene and Public Health, Baltimore. Women were recruited as study participants from patients admitted to participating medical centers with a diagnosis of rupture of the chorioamniotic membranes before the onset of labor at an estimated gestational age of <37 weeks. This estimate of gestational age was based on last menstrual period, early pregnancy tests, physical examination, and available ultrasonographic measurements of the fetus. Control subjects were obtained among women treated in local prenatal clinics or offices during the same period. Singleton controls who had intact membranes at the time of interview were matched to cases on the basis of age (within 4 years), gestational age (within 3 weeks), parity (nulliparous or multiparous), service (private or clinic), and history of cesarean section (yes or no).

Three hundred forty-one women with preterm premature rupture of membranes who met the inclusion criteria were enrolled in the study. The control subjects of the first 58 cases in Boston were enrolled according to different criteria than were subsequently used in the other centers; therefore these nonstandard controls were not entered into the data base. The 58 cases of preterm premature rupture of membranes were entered because the data were collected with the standard enrollment criteria and questionnaire. Nineteen of the 272 matched controls subsequently recruited for the study became ineligible because of ruptured membranes before 37 weeks' gestation ($n = 10$) or twin delivery ($n = 9$), leaving 253 eligible controls included in the final analysis. Control women who were excluded and those remaining in the study were similar in regard to demographic characteristics. A pretested standardized questionnaire was used by all study centers to interview cases and controls. Interviews were conducted by trained obstetrics and gynecology nurses who were not masked to the patient's clinical status. The study

Table I. Distribution of cases and controls by study center

Center	Cases		Controls	
	No.	*%*	*No.*	*%*
Boston	133	39.0	75	29.6
Minneapolis	14	4.1	0	0.0
Pittsburgh	87	25.1	85	33.6
San Antonio	59	17.3	46	18.2
Seattle	17	5.1	17	6.7
Vermont	31	9.1	30	11.9
TOTAL	341	100.0	253	100.0

was reviewed and approved by the institutional review boards at each participating institution.

Study variables. Information in the study was classified into categories as demographic variables, medical history (diabetes mellitus, anemia, renal disease, hypertension), gynecologic history (sexually transmitted disease, infertility, reproductive history), obstetric history (therapeutic abortion, spontaneous abortion, abnormality of uterus, route of delivery), current pregnancy history (prenatal care, maternal infection, physical activity, medication usage), and sexual behavior (number of sexual partners, age at first intercourse, sexual activity).

Premature rupture of membranes was defined as amniorrhexis >1 hour before the onset of labor. When cases and controls were questioned about obstetric history, preterm delivery was defined as delivery of an infant weighing <2500 gm at birth. This definition might include some infants that are born after more than 37 weeks from the last menstrual period but are below the 3rd percentile in weight (small for gestational age), but the definition was chosen as the most objectively reproducible. Hypertension was defined as an increase in systolic blood pressure ≥30 torr and an increase in diastolic blood pressure of ≥15 torr over the minimum blood pressure in the pregnancy. Anemia was defined as a hematocrit ≤30 vol %. Diabetes refers only to those patients who required insulin for glucose control before or during pregnancy.

Statistical analysis. In the univariate analysis, Fisher's exact probability test and χ^2 were used when appropriate to determine the statistical associations between case-control status and qualitative variables. The student *t* test was used to compare case-control differences for continuous variables. Multiple logistic regression was used for multivariate analysis to adjust simultaneously for covariates. Unconditional logistic regression was performed for the unbalanced group matching in which matching variables were included in the multivariate model to study their confounding effect, if present. Variables found to be statistically significant in the univariate analysis were entered in the multivariate model with other variables to examine their independent effects. Unless otherwise stated, the statistically significant differences were represented by a two-sided p value <0.05. Probability values shown in the tables were calculated by a 2 × N contingency table. The calculations were performed by SAS statistical program (Cary, N.C.).

Results

The distribution of cases and controls is shown by study center in Table I. Because the Minneapolis center contributed only 4% of the cases, the data were analyzed with and without Minneapolis cases; no substantial differences were found in the results. The demographic characteristics of the population are shown in Table II. The only significant difference was the greater proportion of cases of preterm premature rupture of membranes in all of the unmarried categories.

Physical and dietary comparisons of the cases and controls revealed no significant differences between the groups. Cases had a mean height of 161.8 ± 7.6 (SD) cm with a mean prepregnancy weight of 59.0 ± 11.1 kg and a mean weight of 76.1 ± 14.4 kg on admission with preterm premature rupture of membranes. Controls had a mean height of 163.6 ± 7.9 cm with a mean prepregnancy weight of 61.8 ± 14.9 kg and a mean weight of 73.3 ± 15.0 kg at the time of interview. There were no significant differences in ethanol ingestion between cases and control subjects even when subdivided into use of beer, wine, or distilled liquor and when subdivided by trimester. No significant differences were found between the groups in use of prenatal medications, antibiotics, prenatal vitamins, or oral iron supplements; however, the frequency of reported maternal anemia was greater in cases (16.2%) than in controls (9.2%) to a significant degree ($p = 0.01$). Measurements on hospital admission revealed that a hematocrit < 32 vol/dl was present in 20% of women with preterm premature rupture of membranes and 4% of control women. A hematocrit <30 vol/dl was present in 8% of women with preterm premature rupture of membranes and 2% of controls ($p < 0.05$).

Univariate comparison of the gynecologic and obstetric history revealed no significant differences be-

Table II. Percent distribution of demographic characteristics in cases and controls

Factor	*Cases (N = 341)*	*Controls (N = 253)*	*p Value**
Age			
≤ 20 yr	15.4	11.2	0.70
21-25 yr	27.6	31.2	
26-30 yr	27.9	27.1	
31-35 yr	21.5	24.3	
36-40 yr	7.6	5.7	
Race			
White	70.0	71.9	0.94
Black	15.0	13.1	
Hispanic	13.8	14.2	
Oriental	0.6	0.4	
Other	0.6	0.4	
Marital status			
Never married	16.8	9.2	0.005
Single, living together	6.6	5.4	
Married	70.6	81.9	
Separated	3.3	0.4	
Divorced	1.8	1.2	
Socioeconomic status			
Hollingshead index			
High executive	9.3	13.6	0.42
Business manager	9.0	10.8	
Administrative personnel	13.5	11.2	
Clerical salesman	8.7	11.2	
Skilled worker	14.4	15.8	
Semiskilled worker	14.7	12.7	
Unskilled worker	11.7	8.9	
Income, annual			
< $15,000	39.9	39.2	0.24
$15,000-$30,000	33.6	31.9	
> $30,000	23.1	27.7	
Type of health care			
Private pay	4.8	9.2	0.38
Medical insurance	59.6	64.6	
Maternal and infant care program	1.5	1.5	
Low-income partial pay	13.6	14.2	
Welfare	18.7	10.5	

*p Value of χ^2 calculated by 2 × N contingency table; missing data are not shown in this table.

tween cases and controls in the number of previous term neonates delivered, previous spontaneous abortions, previous ectopic pregnancies, all previous gynecologic surgical procedures, and specifically previous cone biopsies of the cervix. When a history of infertility was sought by asking whether the patient had ever attempted to conceive without success for >1 year or if she had undergone medical or surgical therapy for infertility, 15.9% of cases and 10.4% of controls answered affirmatively ($p = 0.11$).

In univariate analysis significant differences in gynecologic and obstetric history were found between cases and controls in the total number of pregnancies, in parity, in number of previous preterm neonates delivered, in number of previous preterm neonates with premature rupture of membranes, in the number of previous curettage procedures, and in the number of cases with two previous elective abortions (Table III). When the patients and controls with two and with three or more elective abortions are combined and compared with those having a history of zero or one elective abortion, however, 7.5% of the cases and 3.1% of control subjects have had two or more elective abortions ($p = 0.08$). There was a minimal increase in the frequency of history of maternal diethylstilbestrol ingestion in cases of preterm premature rupture of membranes compared with controls, but the reason for the greater number of "unknown" responses in cases of preterm premature rupture of membranes was not clear. Because of the larger proportion of these "unknown" responses in cases, however, exposure to diethylstilbestrol in utero was related to preterm premature rupture of membranes ($p = 0.05$) in the univariate analysis and in the multivariate analysis.

Sexual behavior and its effects were studied with a series of questions, but only duration of time between membrane rupture and last sexual intercourse was significantly different in cases and controls (Table IV). Fewer cases (36.4%) than controls (53.6%) reported sexual intercourse within 1 week of the interview. The mean age at first intercourse was 18 years in both cases and controls. There was no difference between the

Table III. Percent distribution of gynecologic and obstetric variables

Factor	*Cases (N = 341)*	*Controls (N = 253)*	*p Value**
Total No. of pregnancies			
0	4.8	6.9	0.05
1	29.4	29.6	
2	24.6	30.0	
≥ 3	41.2	33.5	
Parity			
0	6.9	8.5	0.05
1	44.7	41.2	
2	24.0	33.5	
≥ 3	24.3	16.0	
Previous preterm neonate			
Yes	17.5	7.0	0.003
No	82.5	93.0	
PPROM with previous preterm neonate			
Yes	13.7	3.2	0.023
No	3.8	4.0	
Previous dilatation and curettage			
0	56.5	66.5	0.04
1	23.7	19.6	
≥2	18.9	13.1	
Previous elective abortion			
0	76.0	78.9	0.01
1	16.5	18.0	
2	7.5	2.3	
≥ 3	0.0	0.8	
Exposure to DES in utero			
Yes	4.8	2.3	0.0002
No	73.6	87.3	
Unknown	21.6	10.4	

PPROM, Preterm premature rupture of membranes, *DES*, diethylstilbestrol.
**p* Value of χ^2, calculated by 2 × N contingency table.

Table IV. Percent distribution of duration between last intercourse and rupture of membranes

Duration	*Cases (N = 341)*	*Controls (N = 253)*	*p Value**
<48 hr	7.8	9.3	0.001
48 hr–1 wk	28.6	44.3	
1 wk–1 mo	29.2	30.7	
>1 mo	34.3	15.7	

**p* Value of χ^2 calculated by 2 × 4 contingency table.

groups in the total number of previous sexual partners, in the frequency of oral-genital sexual contact, or in the frequency of sexually transmitted disease either preceding the pregnancy or occurring during the index pregnancy. Specific questions about a history of pelvic inflammatory disease, genital *Herpes simplex* infections, gonorrhea, *Trichomonas vaginalis* infections, *Candida albicans* vaginitis, and "nonspecific vaginitis" either before or during the index pregnancy failed to elicit any significant differences between groups. When *C. albicans* vaginitis and nonspecific vaginitis were excluded from consideration, the frequency of sexually transmitted diseases by history during the current pregnancy was 12.8% in cases of preterm premature rupture of membranes and 9.2% in controls ($p = 0.46$).

Patients with preterm premature rupture of membranes were asked about their activity at the time membranes ruptured. Fifty percent were asleep at the time of preterm premature rupture of membranes, 18% were sitting, and 26% were engaged in light or moderate activity. Only 1% of the cases were engaged in strenuous activities such as heavy lifting or jogging at the time of preterm premature rupture of membranes, and 5% could not recall their level of activity.

Characteristics most highly associated with preterm premature rupture of membranes in univariate analysis are presented in Table V. Vaginal bleeding in at least one trimester of pregnancy, cigarette smoking, anemia, hypertension, or diabetes during the index pregnancy were all associated with an increased risk of preterm premature rupture of membranes in the univariate analysis. Vaginal bleeding in at least one trimester of pregnancy occurred in 41.4% of cases of preterm premature rupture of membranes and in 17.3% of control women ($p = 0.0001$). In the multivariate analysis, previous preterm delivery, cigarette smoking, and vaginal bleeding during the index pregnancy were significantly associated with an increased risk of preterm premature

Table V. Percent distribution* of risk factors for preterm premature rupture of membranes

Risk factor	*Cases*	*Controls*	*p Value†*
Bleeding during index pregnancy			
No	58.6	82.7	0.0001
Yes			
Only one trimester	29.4	15.0	
More than one trimester	12.0	2.3	
Cigarette smoking during pregnancy			
Nonsmoker	40.2	48.9	0.0006
Stopped before pregnancy	16.8	23.5	
Stopped during pregnancy	6.0	6.2	
Still smoking	36.9	21.4	
Hypertension or diabetes during pregnancy			
Yes	26.0	16.2	0.03
No	74.0	83.8	
Anemia during index pregnancy			
Yes	16.2	9.2	0.01
No	83.8	90.8	

*Proportion of missing data not reported.
†p Value of χ^2 or Fisher's exact test where appropriate.

Table VI. Adjusted odds ratio of risk factors for preterm premature rupture of the membranes

Factor	*Odds ratio**	*95% Confidence limit*
Previous preterm delivery		
No	1.00	
Yes	2.48	1.40, 2.48
Cigarette smoking during this pregnancy		
None	1.00	
Smoked but stopped	1.58	0.77, 3.27
Presently smoking	2.08	1.37, 3.13
Bleeding during this pregnancy		
None	1.00	
During first trimester	2.38	1.47, 3.86
During second trimester	4.42	1.62, 12.03
During third trimester	6.44	1.81, 22.91
More than one trimester	7.43	2.16, 25.60

*Adjusted for income and race.

rupture of membranes (Table VI). Vaginal bleeding in any trimester, especially in the third trimester or in more than one trimester, is therefore an important marker for preterm rupture of membranes with a greater than sevenfold increase in risk for women with bleeding in more than one trimester.

Similarly, cigarette smoking during pregnancy was found significantly more often in cases with preterm premature rupture of membranes than in controls. Some smoking had occurred during pregnancy in 43.0% of cases but only 27.7% of controls ($p = 0.0006$). In the multivariate model there was a dose-response relationship observed with a 2.1-fold risk of preterm premature rupture of membranes in those women who had not stopped smoking. A history of previous preterm delivery was associated with a 2.5-fold risk of preterm premature rupture of membranes by multivariate analysis.

Comment

This study represents a large analytic epidemiologic study of risk factors for preterm premature rupture of the fetal membranes. Several features of this study strengthen the results and permit their application to a broad spectrum of situations and populations. First, the study includes patients from populations that are geographically, ethnically, and socioeconomically diverse. Second, the questionnaire used to obtain data was extensive and sophisticated. For example, the use of the Hollingshead index to delineate socioeconomic status is more precise than many more simple methods. In addition, the questionnaire was field-tested and improved in Boston before multicenter use. Third, the use of multivariate statistical analysis by logistic regression permits identification of significant independent variables. The results confirm and amplify some previous findings, but most important, they provide a basis

for further studies of methods to prevent and manage this vexing problem.

In agreement with other studies,[2, 3, 5, 6] we found that antepartum vaginal bleeding, history of preterm delivery, and cigarette smoking were related to an increased risk of preterm premature rupture of membranes. In a report published since we conducted our study, the association between smoking one or more packs of cigarettes per day and both abruptio placentae and preterm premature rupture of membranes was confirmed in a population of 30,596 women from the Northern California Kaiser Permanente Birth Defects Study.[9] In this study women who smoked one or more packs per day had a 2.2-fold increase in the risk of preterm premature rupture of membranes before 33 weeks' gestation and a 1.9-fold increase in abruptio placentae.

Chronic abruptio placentae provides a likely explanation for antepartum vaginal bleeding as a risk factor for preterm premature rupture of membranes. Because patients with preterm premature rupture of membranes are more likely to have hypertension, diabetes mellitus, and a history of cigarette smoking, all of which are risk factors associated with abruptio placentae, chronic abruptio placentae may account for both the vaginal bleeding and for increased uterine irritability and intrauterine pressure. An increase in intrauterine pressure could then cause preterm premature rupture of membranes over a local structural defect at the internal cervical os.[10, 11] However, the possibility of antepartum vaginal bleeding as merely a marker for preterm premature rupture of membranes cannot be excluded. It is possible, that antepartum vaginal bleeding is a separate manifestation of infection or other problem that primarily causes preterm premature rupture of membranes.

An association between preterm premature rupture of membranes, chorioamnionitis, and intrauterine infections has been reported previously.[3, 8] In these studies, *B. fragilis* organisms could be isolated from the cervix, placenta, and amnionic fluid in women with preterm premature rupture of membranes but was not found in controls. Histologic evidence of chorioamnionitis also has been linked to preterm delivery.[12] Recent evidence suggests that histologic evidence of chorioamnionitis can be found in 35% of women with severe abruptio placentae (i.e., those cases requiring immediate delivery).[13] Abruptio placentae could explain both antepartum vaginal bleeding and preterm premature rupture of membranes since preterm premature rupture of membranes and preterm labor probably represent a clinical continuum.

In agreement with two previous studies,[5, 6] we found that cigarette smoking during the index pregnancy increased the risk for preterm premature rupture of membranes. However, this finding contradicted results from a survey of 4440 women in South Carolina.[7] Cigarette smoke contains both carbon monoxide and nicotine, which may have a deleterious effect on the fetoplacental unit. Carbon monoxide combines with maternal and fetal hemoglobin with an affinity 210 times greater than that of oxygen, and it shifts the oxygen dissociation curve of fetal hemoglobin so that fetal oxygenation is reduced. Because nicotine causes arteriolar constriction, it could cause uterine decidual ischemic necrosis and subsequent abruptio placentae. Further studies of this proposed mechanism are necessary.

The increased risk of preterm premature rupture of membranes in women who continue smoking during pregnancy offers an exciting possibility for intervention. Both the dose-response relationship and the magnitude of the risk estimates suggest that pregnant women who smoke should be encouraged to stop smoking to decrease their risk of preterm premature rupture of membranes. A randomized clinical trial would be necessary to determine the magnitude of the decrease in risk of preterm premature rupture of membranes that can be achieved by the cessation of smoking.

Exclusion of the ineligible control subjects (24%) was a major limitation of this study. The comparisons of remaining controls with those excluded, however, revealed no substantial differences in demographic characteristics or risk factors between the two groups. Bias, if present, should therefore be minimal. The statistical power of this study is weakened by the reduced sample size, but the results and inferences should not be affected.

In summary, this study found that antepartum vaginal bleeding, history of preterm labor, and cigarette smoking during the index pregnancy are strong risk factors for preterm premature rupture of membranes. Further studies are necessary to explain these findings, but this study provides evidence that some action to reduce the occurrence of preterm premature rupture of membranes and its neonatal sequalae is possible. Strategies to help pregnant women cease cigarette smoking should be pursued vigorously, especially in patients with prior preterm premature rupture of membranes. In addition, precise determination of gestational age and careful antepartum fetal assessment should be performed in cases of antepartum vaginal bleeding in anticipation of the preterm premature rupture of membranes associated with such bleeding. Finally, methods to prevent preterm premature rupture of membranes should be focused on women at increased risk for the condition.

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Necrotizing fasciitis of the total abdominal wall after sterilization by partial salpingectomy

Case report and review of literature

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A case of necrotizing fasciitis with full-thickness loss of the entire abdominal wall is reported after an uncomplicated sterilization by bilateral partial salpingectomy through a minilaparotomy incision in a healthy young patient. Salvage was accomplished by early wide surgical debridement and multiple reconstructive procedures. (AM J OBSTET GYNECOL 1990;162:138-9.)

Key words: Necrotizing fasciitis, total abdominal wall

Necrotizing fasciitis is a rapidly progressive, often fatal soft tissue infection involving the superficial and deep fascia with secondary involvement of the overlying skin as thrombosis of nutrient vessels occurs. The underlying muscle is spared until its entire facial envelope is affected late in the process.[1]

There are reports in the gynecologic literature of necrotizing fasciitis occurring after Bartholin abscesses,[2] vaginal delivery,[3-9] cesarean section,[3] abdominal hysterectomy,[10] sterilization by bilateral total salpingectomy,[11] and diagnostic laparoscopy[12] and spontaneously in the endopelvic fascia.[13] There are no reports of necrotizing fasciitis after sterilization by bilateral partial salpingectomy.

Case report

A 41-year-old, previously healthy woman was seen in the emergency room with severe abdominal pain, nausea, and vomiting. She had undergone elective sterilization by bilateral partial resection and ligation of the fallopian tubes through a suprapubic minilaparotomy incision (Pomeroy procedure) the day before. In the emergency room her temperature was 94.6° F, pulse 130 beats/min, respirations 48 breaths/min, and blood pressure 70/50 mm Hg.

Physical examination revealed a diffusely tender abdomen with guarding and rebound. Bowel sounds were absent, and the transverse suprapubic incision was slightly swollen and mildly erythematous with a large amount of drainage. The platelets count was 157,000/mm^3. Initial electrolytes were normal except for a carbon dioxide level of 15.3 mEq/L. Blood urea nitrogen and creatinine levels were 33 and 3.0 mg/dl, respectively. Liver function and amylase level were normal, whereas creatine phosphokinase was elevated at 972. Arterial blood gas levels on 6 L of oxygen via nasal cannula included Po_2 of 44.9 mm Hg, Pco_2 of 32.8 mm Hg, pH of 7.32, and bicarbonate of 16.8 mEq/L.

The patient was transferred to the intensive care unit; Swan-Ganz catheter (Baxter Edwards, Irvine, Calif.) and arterial lines were placed and fluid resuscitation was instituted. The patient received intravenous corticosteroids and broad-spectrum antibiotic coverage including ceftazidime, aztreonam, and metronidazole. Disseminated intravascular coagulopathy developed shortly after admission, and appropriate blood component therapy was instituted. Her condition stabilized to permit operation approximately 18 hours after emergency room presentation.

On operation extensive necrotizing fasciitis involving the entire abdominal wall without perforation of the bowel or uterus was found. The fallopian tubes showed evidence of recent surgical interruption with suture material in place. Abdominal hysterectomy with bilateral salpingo-oophorectomy and wide debridement resulted in a full-thickness defect of the entire abdominal wall.

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Cultures of infected abdominal wall tissue, urine, and blood grew an *Escherichia coli* organism sensitive to all antibiotics tested; anaerobic bacteria were not present. Postoperative treatment inclded a combination of piperacillin-gentamicin-clindamycin. The patient's condition stabilized, and further surgical debridement of the abdominal wall was required on the tenth hospital day with placement of a Vicryl mesh (Ethicon, Inc., Somerville, N.J.) over the omentum to slow the massive abdominal fluid loss.

Multiple reconstructive procedures began 15 days after the initial operative intervention. Reconstruction with bilateral tensor fascia lata myocutaneous flaps and polyglactin (Vicryl) mesh replacement was performed. Additional debridement and split-thickness skin grafting closed the abdominal defect completely. During the following year tissue expansion with flap advancement over polypropylene (Prolene, Ethicon) mesh to prevent abdominal hernia formation was done. Suction-assisted lipectomy to tailor the flaps was performed to complete the reconstruction.

Comment

Necrotizing fasciitis has been reported in all areas of the body.[14] There is no significant age or sex predilection.[15, 16] Clinically severe pain, swelling, and ill-defined cellulitis exhibit early. The overlying skin anesthetizes as a result of cutaneous nerve necrosis. Nutrient vessels to the skin are destroyed, causing the characteristic dull blue-gray areas, and blisters filled with hemorrhagic fluid. Tissue examination demonstrates widespread undermining of the skin, gray attenuated fascia, and pockets of serosanguineous fluid. Muscle necrosis develops later. Severe systemic toxicity accompanies these local findings.

The prognosis of necrotizing fasciitis directly relates to the speed of the diagnosis and wide surgical debridement of all devitalized tissue.[14] Once suspected, an incision should be made down to the underlying fascia. Extensive undermining of the skin confirms the diagnosis. Multiple linear incisions through the skin and subcutaneous fat are made until normal deep fascia is encountered. Debridement is adequate when finger dissection can no longer separate the subcutaneous fat from the fascia.[15, 17] Frequent evaluation of the wound by probing at the fascial level with a gloved finger is mandatory after operation.[17]

Empiric antimicrobial coverage should be based on the initial Gram stain results. If the smear shows a mixed picture, high-dose penicillin G or a semisynthetic penicillin to provide coverage against the streptococci plus an aminoglycoside or extended-spectrum cephalosporin for the *Enterobacteriaceae* infection and anaerobic coverage (such as clindamycin, chloramphenicol, metronidazole, imipenem-cilastatin, or β-lactamase–inhibiting penicillin for *Bacteroides fragilis* infection should be instituted pending culture results. If the smear reveals streptococcal organisms only, penicillin G is the antibiotic of choice. If an additional staphylococcal infection appears, use of a penicillinase-resistant penicillin such as oxacillin or nafcillin is recommended.[1]

The source of bacterial inoculum in our case was most likely the patient's skin. The upper genital tract is normally sterile, and the patient exhibited no symptoms or clinical evidence of salpingitis at the initial sterilization procedure. Although no prophylactic antibiotics were used, they are not usually indicated for routine tubal sterilization in an otherwise healthy patient without evidence of pelvic inflammation.[18] Infection should rarely occur in a patient with a competent immune system.

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Relationship between plasma calcium fractions, other bone-related variables, and serum follicle-stimulating hormone levels in premenopausal, perimenopausal, and postmenopausal women

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The study comprises 186 untreated normal premenopausal, perimenopausal, and postmenopausal women in whom we measured serum follicle-stimulating hormone and a number of bone-related plasma and urinary variables. The calcium fractions in the plasma were calculated from the total calcium, albumin, globulin, anion gap, and bicarbonate concentrations. With a level of follicle-stimulating hormone within the reference range (up to 20 U/L) to define the premenopausal state, we confirmed previously reported menopausal rises in plasma calcium, phosphate, alkaline phosphatase, and bicarbonate, and in urinary calcium and hydroxyproline. However, inspection of the data, and *t* testing at different follicle-stimulating hormone criteria showed that these changes in bone-related variables did not generally occur until the level of follicle-stimulating hormone exceeded approximately 50 U/L. The plasma alkaline phosphatase level rose earlier than the other variables and was significantly elevated in subjects with follicle-stimulating hormone values above 30 U/L. The rise in plasma calcium was mainly a result of a rise in the ultrafiltrable fraction, which in turn was accounted for by rises in the ionized and complexed fractions, of which the complexed fraction was the most significant and proportionately the largest. The rise in the complexed fraction was accounted for by the increase in plasma bicarbonate. (Am J Obstet Gynecol 1990;163: 140-5.)

Key words: Menopause, plasma calcium, ionized calcium, follicle-stimulating hormone, urinary calcium

Although there are well-recognized changes in calcium metabolism at or about the time of the menopause, neither the primary event nor the stage in the climacteric at which it occurs has yet been established. We now report a cross-sectional study of normal premenopausal, perimenopausal, and postmenopausal women in whom we have measured the main plasma and urinary bone-related variables and compared them with the plasma follicle-stimulating hormone (FSH) level determined at the same time.

Material and methods

The series comprised 186 untreated normal women aged 32 to 60 years who first came to a menopause clinic with premenstrual tension or menopausal-type complaints, who were investigated by a standard protocol (see below), and who had no evidence of bone, kidney, or liver disease. Patients receiving corticosteroids or diuretics were excluded. Sixty-four of the women were still menstruating, albeit many of them irregularly; 17 had ceased menstruating within the past year; 52 had been amenorrheic for more than a year; 25 had had oophorectomy; and 28 had undergone hysterectomy with preservation of at least one ovary.

All the patients were tested at 9 AM after a 12-hour fast and after discarding their overnight urine samples. A venous blood sample obtained without a tourniquet and a fresh urine sample were collected. We measured FSH in the serum by radioimmunoassay; calcium, albium, globulin, alkaline phosphatase, sodium, potassium, chloride, and bicarbonate in the plasma were measured on the Technicon SMAC II (Tarrytown, N.Y.) with computer. The anion gap was calculated as the difference between the sum of the sodium and potassium concentrations and the sum of the chloride and bicarbonate concentrations. Calcium in the urine was measured on a centrifugal analyzer (Cobas-Bio Roche, Sydney, Australia), sodium by ion-selective electrode,

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Table I. Mean ages and serum levels of FSH (±SD) in women grouped by menstrual status

		Amenorrhea			
	Menstruating (n = 64)	*<1 yr (n = 17)*	*>1 yr (n = 52)*	*Oophorectomy (n = 25)*	*Hysterectomy (n = 28)*
Age (yr)	44.7 ± 5.1	49.3 ± 4.1	53.1 ± 5.2	47.8 ± 9.2	52.2 ± 5.7
FSH (U/L)	28.7 ± 26.0	86.1 ± 38.0	114.0 ± 26.8	109.0 ± 35.7	93.2 ± 48.1
Time since menopause (yr)	—	—	5.6 ± 0.5	7.3 ± 1.2	—

Table II. Mean values of significantly different measured variables in 37 women with FSH values up to 20 U/L and 149 with FSH values above 20 U/L

	Mean value (±SE)			
Variable	*FSH<20 U/L*	*>FSH 20 U/L*	*t*	*p*
Age (yr)	42.9 ± 0.8	50.1 ± 0.6	5.3	<0.001
Plasma Ca (mmol/L)	2.341 ± 0.014	2.378 ± 0.0066	2.3	<0.05
Plasma P (mmol/L)	0.93 ± 0.033	1.03 ± 0.013	2.7	<0.01
Plasma ALP (U/L)	58.4 ± 2.7	71.0 ± 1.7	3.8	<0.001
Plasma sodium (mmol/L)	138.8 ± 0.30	139.6 ± 0.14	2.4	<0.05
Plasma potassium (mmol/L)	3.67 ± 0.065	3.83 ± 0.023	2.2	<0.05
Ultrafiltrable Ca (mmol/L)*	1.533 ± 0.0076	1.561 ± 0.0040	3.3	<0.002
Complexed Ca (mmol/L)*	0.356 ± 0.0037	0.369 ± 0.0018	3.1	<0.005
Ionized Ca (mmol/L)*	1.177 ± 0.0059	1.192 ± 0.0029	2.3	<0.05
Urine Ca/Cr	0.17 ± 0.018	0.25 ± 0.012	3.2	<0.002
Urine OHPr/Cr	14.3 ± 0.81	18.1 ± 0.50	4.0	<0.001
Ca/Cr (Na-corrected)	0.060 ± 0.016	0.12 ± 0.0011	3.2	<0.005

Ca, Calcium; *P*, phosphorus; *ALP*, alkaline phosphatase; *Ca/Cr*, calcium/creatinine; *OHPr/Cr*, hydroxyproline/creatinine; *Na*, sodium. Not significant: plasma albumin, globulin, bicarbonate, chloride, anion gap, protein-bound calcium, and urine sodium.
*Calculated.

hydroxyproline by the method of Bergman and Loxley,[1] and creatinine by the Jaffé reaction. Calcium and sodium excretion were expressed as the molar ratio to creatinine, and hydroxyproline excretion as millimole per micromole of creatinine. Calcium excretion was corrected for sodium by assuming a sodium/calcium molar ratio of 100:1.[2, 3] The reference range of FSH in premenopausal women in our laboratory is up to 20 U/L.

The calcium fractions in the plasma were calculated from the following equation by an iterative program based on the binding coefficients derived from our previous study of 556 normal postmenopausal women[4]:

$$[Ca^{++}] = T_{Ca} - \frac{0.01257[Ca]T_{Alb}}{1 + 0.01257[Ca^{++}]} - \frac{0.0049[Ca]T_{Glb}}{1 + 0.0049[Ca^{++}]} - \frac{0.00835[Ca]T_{AnG}}{1 + 0.00835[Ca^{++}]} - \frac{0.00759[Ca]T_{Bic}}{1 + 0.00759[Ca^{++}]}$$

where $[Ca^{++}]$ represents the plasma ionized calcium and T_{Ca} total calcium concentration in millimoles per liter, Alb and Glb represent plasma albumin and globulin in grams per liter, and AnG and Bic represent the anion gap and bicarbonate in millimoles per liter.

Statistical analysis was performed by one-way analysis of variance and by two-tailed *t* test using Minitab program 5.1 (Minitab, Inc., State College, Pa.) on a personal computer.

Results

The mean serum FSH levels in the five clinical groups are shown in Table I. Even in the 64 women who were still menstruating the mean FSH level was 28.7 U/L; 30 of the individual values were above the reference range. In all other groups, all FSH values were above the reference range except in three women aged 35, 40, 52 respectively, who had undergone simple hysterectomy.

The cases were then classified into premenopausal and perimenopausal or postmenopausal groups on the basis of their FSH level; up to 20 U/L was used as the criterion of the premenopausal state. There were 37 such women, of whom 34 were still menstruating (three were the simple hysterectomy cases mentioned previously). The mean values of the measured variables that differed significantly between the groups with normal and raised FSH levels are shown in Table II. The

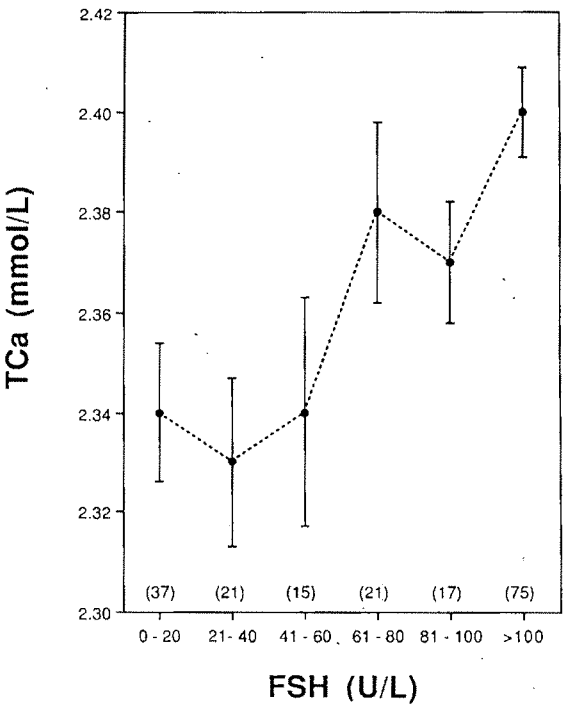


Fig. 1. Mean total plasma calcium *(TCa)* ± SE in patients grouped by FSH levels (the numbers in each group are indicated).

plasma calcium, phosphate, alkaline phosphatase, sodium, calculated complexed and ultrafiltrable calcium, urine calcium, and hydroxyproline were all significantly raised in the group with raised FSH.

Because inspection of the data suggested that these changes in variables occurred at a level of FSH higher than 20 U/L, the cases were then classified into six groups according to their FSH levels: 1 to 20, 21 to 40, 41 to 60, 61 to 80, 81 to 100, and >100 U/L, and the mean values of the measured variables were calculated in each group. Inspection of these data (of which the plasma calcium is shown in Fig. 1 and eight further examples in Figs. 2 and 3) indicated that the critical FSH value was approximately 50 to 60 U/L. Each variable was therefore retested at different FSH criteria (in steps of 5 U/L) to establish the criterion that yielded the highest t value when the means up to and above each criterion were compared. The results are shown in Table III. The variables in Table III are essentially the same as those in Table II except that the differences in bicarbonate and calculated protein-bound calcium, which were not significant at a level of FSH of 20 U/L, became significant at higher FSH criteria. For all the variables except plasma alkaline phosphatase, the FSH criteria for optimum discrimination between the mean values of variables at low and high FSH levels range from 55 to 70 U/L; for alkaline phosphatase the optimum criterion is 30 U/L.

It is also clear from Tables II and III (and from the figures) that the higher FSH criteria yield larger and more significant differences in most variables than are seen at an FSH level of 20 U/L. Thus the total plasma calcium differs only just significantly ($p < 0.05$) and by only 0.037 mmol/L when women with FSH values up to and above 20 U/L are compared; at an FSH criterion of 65 U/L, the absolute difference becomes 0.053 mmol/L and the statistical significance of the p value is reached at <0.001. Most of the t values for the other variables are also greater at criteria of about 60 U/L than at 20 U/L.

To confirm that the break point actually occurred at an FSH level of approximately 60 U/L, we performed one-way analysis of variance on the three lowest FSH groups and the three highest FSH groups separately. With none of the measured variables was the F value significant within either the lower or upper three FSH groups.

Comment

These observations can be separated into two categories: the nature of the change in calcium metabolism at the menopause and the stage of menopause at which it occurs. They are dependent on the validity of our calculation of the plasma calcium fractions, which represents a possible source of error.

We noted again the rise in plasma calcium at the menopause that we first reported in the early 1970s[5, 6] and has since been amply confirmed.[3, 7-11] It has always been assumed that this rise in total calcium reflects a rise in the ionized fraction, as has been reported by some workers,[8] but recent work has not confirmed this.[7, 9-1] We have previously shown that the ionized calcium calculated from the total plasma calcium and the concentrations of albumin, globulin, bicarbonate, and "anion gap" reflects very closely the measured ionized calcium.[1] In our previous study the rise in plasma calcium at the menopause was essentially caused by a rise in the complexed fraction. In this study of a different group of subjects, the rise in total calcium of 0.053 mmol/L (2.3%) when the FSH exceeds approximately 60 U/L is comprised of 0.017 mmol/L in the protein-bound fraction (2.1%) and the remainder almost equally divided in absolute terms between the ionized calcium (which rises 2.0%) and the complexed calcium (which rises 4.5%). These may seem to be small changes but the rise in ultrafiltrable calcium is more than enough to account for the rise in the fasting urinary calcium/creatinine ratio of 0.10. The rise in filtered calcium (0.037 mmol/L) is equivalent to about 0.26

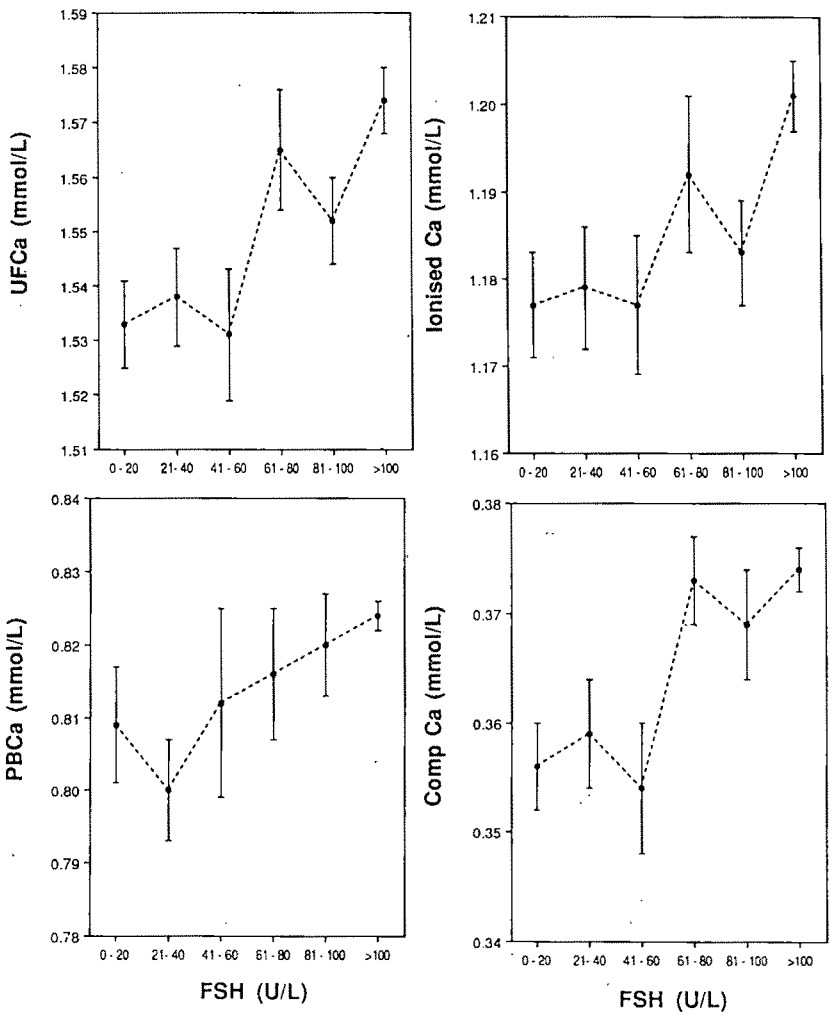


Fig. 2. Mean values ± SE of calculated ultrafiltrable calcium *(UFCa)*, ionized calcium, protein-bound calcium *(PBCa)*, and complexed calcium *(CompCa)* in the same subjects shown in Fig. 1.

Table III. Mean values of measured variables (± SE) in subjects below and above the FSH criterion yielding the highest t value

Variable	*FSH criterion (U/L)*	*Below FSH criterion*	*Above FSH criterion*	*t*	*p*
Total Ca (mmol/L)	65	2.340 ± 0.0093 (n = 73)	2.393 ± 0.0073 (n = 113)	4.4	<0.001
Phosphate (mmol/L)	70	0.96 ± 0.014 (n = 82)	1.07 ± 0.013 (n = 104)	5.5	<0.001
Alkaline phosphatase (U/L)	30	55.5 ± 2.5 (n = 45)	72.4 ± 1.7 (n = 141)	5.6	<0.001
Bicarbonate (mmol/L)	65	27.9 ± 0.23 (n = 78)	28.7 ± 0.20 (n = 108)	2.7	<0.01
Sodium (mmol/L)	65	139.1 ± 0.20 (n = 78)	139.8 ± 0.16 (n = 108)	2.8	<0.01
Potassium (mmol/L)	65	3.72 ± 0.037 (n = 78)	3.85 ± 0.028 (n = 108)	2.7	<0.01
Protein-bound Ca (mmol/L)*	60	0.805 ± 0.0052 (n = 73)	0.822 = 0.0037 (n = 113)	2.6	<0.02
Ultrafiltrable Ca (mmol/L)*	65	1.534 ± 0.0050 (n = 78)	1.571 ± 0.0046 (n = 108)	5.4	<0.001
Ionized Ca (mmol/L)	70	1.177 ± 0.0038 (n = 82)	1.198 ± 0.0033 (n = 104)	4.1	<0.001
Complexed Ca (mmol/L)*	65	0.357 ± 0.0025 (n = 78)	0.373 ± 0.0020 (n = 108)	5.0	<0.001
Urine Ca/Cr	55	0.17 ± 0.013 (n = 70)	0.27 ± 0.014 (n = 116)	5.0	<0.001
Urine Ca/Cr†	60	0.060 ± 0.012 (n = 73)	0.14 ± 0.013 (n = 113)	4.2	<0.001
Urine OHPr/Cr	55	14.0 ± 0.59 (n = 70)	19.3 ± 0.54 (n = 116)	6.6	<0.001

See Table II for abbreviations. Not significant: plasma albumin, globulin, chloride, anion gap, and urine sodium.
*Calculated.
†Corrected for sodium.

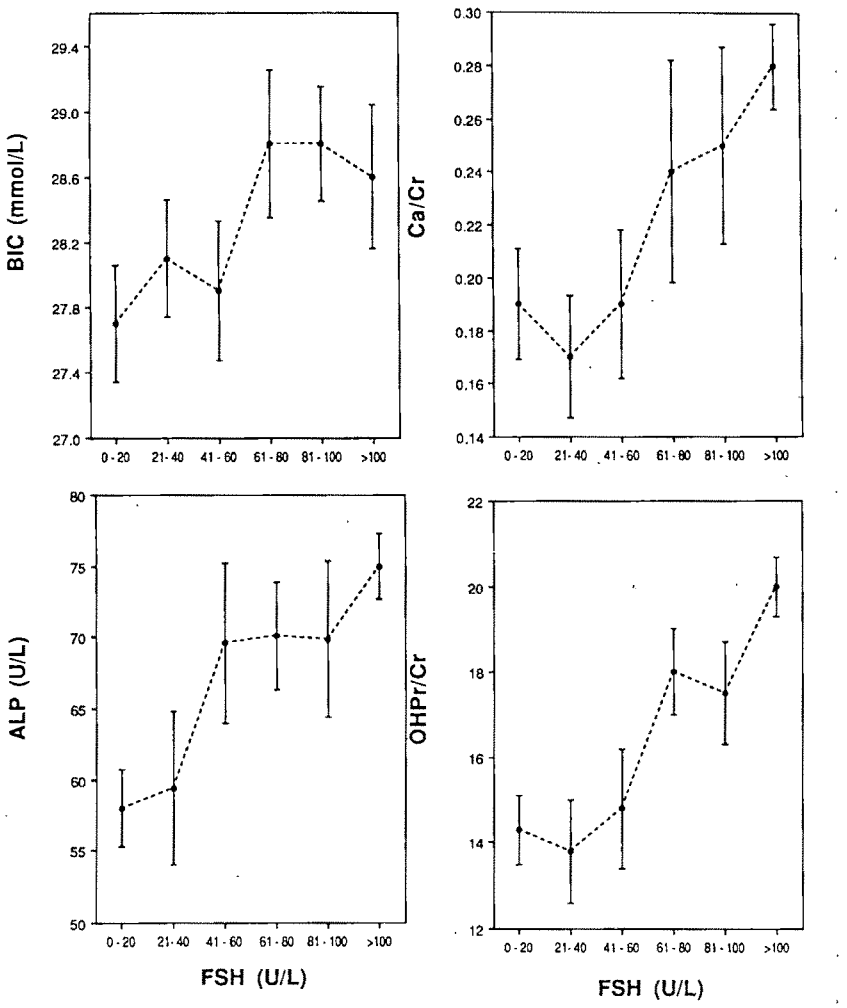


Fig. 3. Mean plasma alkaline phosphatase *(ALP)*, bicarbonate *(Bic)*, urinary calcium/creatinine *(Ca/Cr)*, and hydroxyproline/creatinine *(OHPr/Ca)* in the same subjects shown in Fig. 1.

mmol/hr or 6.2 mmol/day at a glomerular filtration rate of 120 ml/min. Conversely, the rise in urine calcium only amounts to about 1 mmol/day. The increase in excreted calcium could therefore be accounted for by the increase in filtered calcium. The disproportionate rise in the complexed fraction of the plasma calcium is accounted for by the rise in plasma bicarbonate that has been noted previously[12] but has not attracted much interest. It could represent a mild metabolic alkalosis or respiratory acidosis. It is reversible by hormone administration.[11]

The significance of these findings in relation to the pathogenesis of postmenopausal osteoporosis is potentially great. The rise in plasma calcium at the menopause has variously been attributed to increased sensitivity of bone to parathyroid hormone in the absence of estrogen[13, 14] and to a change in the parathyroid gland set point for calcium.[15] Both of these explanations assume a change in the ionized fraction and fail to resolve what we consider to be the central issue: whether the increased urinary calcium after the menopause is the cause or result of the increase in bone resorption. If the rise in plasma calcium is largely a result of a change in the complexed fraction, it can hardly be secondary to increased bone resorption, and this would also explain why parathyroid hormone and 1,25-hydroxyvitamin D_3 levels do not change at the menopause.[16, 17] It also explains the rise in urinary calcium, even if there is no preferential excretion of the complexed fraction, which may be the case. However, interpretation is complicated by the small but significant rise in the ionized calcium fraction in our current data. This cannot be the primary event because it is much too small to explain the rise in the complexed fraction. However, neither can it be argued that the rise in complexed calcium is responsible for the rise in the ionic fraction; quite the reverse appears to be true. Resolution of this problem must await more information about the effect of the menopause on blood pH, which could have a profound effect on the interpretation of these

data, all of which assume a blood pH of 7.4. (It should also be noted that reports of unchanged measured ionized calcium at the menopause have corrected their readings to pH 7.4, whereas those that report a rise in measured ionized calcium have not made this correction.[11])

With regard to the stage of the climacteric at which the calcium changes occur, it is common practice to write and speak of "pre-" and "post-" menopausal women as though they moved abruptly from the one state to the other. This is only true of those who undergo oophorectomy. The remainder generally pass through a perimenopausal phase, when symptoms and hormone levels fluctuate, before they finally become truly postmenopausal. Our data show that the menopausal perturbation in all the bone-related variables except alkaline phosphatase occurs late rather than early (i.e., when the FSH level exceeds about 50 to 60 U/L). This is also implied by the data of Slemenda et al.[18] If we assume that the important hormonal event for bone at the menopause is the fall in estrogen levels, this would seem to imply that the FSH rises in the perimenopause before the estrogens have fallen sufficiently to affect the bone. Is it possible that the perimenopausal rise in FSH (seen in many women who are still menstruating) is a response to low inhibin levels rather than low estrogen levels?[19]

The rise in alkaline phosphatase seems to occur at an FSH level of approximately 40 U/L. It reflects both liver and bone function, but we are not aware of any change in liver function at the menopause. We cannot therefore explain why plasma alkaline phosphatase appears to rise at a slightly lower FSH level than does urine hydroxyproline.

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Survival and outcome of infants weighing <800 grams at birth

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This study reports on two aspects of outcome in a sample of infants whose birth weights ranged from 500 to 799 gm. First, maternal and early neonatal variables were analyzed by means of stepwise logistic regression. Five-minute Apgar score and initial pH were the only variables that predicted mortality at $p \leq 0.05$. Second, the surviving infants were examined at ages ranging from 17 months to 7 years. The majority (72%) had neurologic and/or developmental examinations in the suspect or abnormal range and required rehabilitation or early intervention services. (AM J OBSTET GYNECOL 1990;163:146-50.)

Key words: Prematurity, outcome, survival, extremely low birth weight

Since its inception in the early 1960s, the practice of modern neonatal intensive care has focused on infants with progresively lower birth weights.[1,2] Currently neonatologists are challenged by the improving survival of the extremely low birth weight infant (<1000 gm). Neonatology centers are reporting improving survival rates in this weight group, and attention to the neurodevelopmental outcome of the smallest of these infants, i.e., ≤800 gm, has been the subject of several reports.[3-11] To date, most studies have reported on outcomes of extremely low birth weight infants born from 1975 to 1980, with survival rates ranging from 20% to 50%. Rates of cerebral palsy range from 6% to 15%, and mean intelligence or developmental quotients appear to be lowered in many studies.

This study reports on two aspects of outcome in a sample of extremely low birth weight infants (<800 gm) born between 1980 and 1985: (1) the effect of maternal and immediate postnatal variables on survival and (2) the neurodevelopmental outcome of surviving infants.

Material and methods

Neonatal period. Between January 1980 and December 1985, 184 infants whose birth weights ranged from 500 to 799 gm were admitted to the Perinatology Center of The New York Hospital, a 55-bed neonatal intensive care unit. Forty-five percent of the infants were inborn, and the rest were transferred to the intensive care unit by a neonatal fellow and neonatal paramedic team from our neonatal intensive care unit.

Any infant who was discharged from the neonatal intensive care unit was considered a survivor, whereas all other infants were considered as non-survivors, even if death occurred beyond the first 28 days of life but still before discharge from the neonatal intensive care unit.

An analysis of the medical records of all inborn infants ($N = 80$) was performed to determine whether any maternal or early neonatal variables could predict survival. All inborn mother-infant pairs received intensive obstetric and neonatal care. Neonatal fellows attended all deliveries of extremely low birth weight infants and were responsible for assigning the Apgar scores and for resuscitating and administering subsequent intensive care to these infants. The majority of infants in this weight group did require resuscitation in the delivery room and underwent mechanical ventilation on admission to the intensive care unit. Initial pH values were obtained from the umbilical artery within the first hour of life. The neonatal fellow collected and recorded the data subsequently used for this study. The decision to include only infants born at our institution was made to ensure consistency of medical care and reliability of data collection.

Given that the outcome measure, mortality, was a binary variable, stepwise logistic regression analysis was used to predict mortality as a linear additive function of 21 independent variables. Before this analysis was conducted, the independent variables were examined for multicollinearity, and no serious collinearity problems were found. At each step in the analysis, the independent or predictor variable most strongly associated with mortality, controlling for the variables already in the equation, was entered if it was significantly associated with mortality at the $p \leq 0.05$ level.

Follow-up. An attempt was made to contact all of the

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surviving infants (inborn and outborn) who had been admitted to the neonatal intensive care unit. Forty-one of the 184 infants admitted to the neonatal intensive care unit (22%) were discharged home. Twenty-eight of the surviving infants underwent detailed neurodevelopmental evaluations at a mean age of 37 months (17 months to 7 years), including two children examined at neighboring institutions. Of the remaining 13 children who did not return for evaluation, four had died, two had moved out of the area, and five could not be located, including one child who had been placed for adoption. One child who lived out of the area was reported to attend regular kindergarten and to be receiving speech therapy. One additional child who was not evaluated was known to have cerebral palsy and developmental delay and was not included in the outcome data of this report.

Each child was examined by a developmental pediatrician who obtained a detailed history and performed a physical and neurologic assessment. On the basis of the neurologic assessment, the pediatrician classified each child as normal, suspect (e.g., mild to moderate but not disabling abnormalities of tone and reflexes, presence of abnormal movements), or abnormal (presence of cerebral palsy).

Measurements of length/height, weight, and head circumference were obtained and converted to percentiles by careful extrapolation from a published growth chart.[12] Children seen at <24 months of age were plotted according to their corrected age, whereas the growth measures of children over 2 years of age were not corrected for gestational age. The 50th percentile from the normative data was considered the norm for each group.

In addition, a developmental psychologist tested each child with either the Bayley Scales of Infant Development[13] (with both the Mental Developmental Index and the Psychomotor Developmental Index) or the Stanford-Binet Intelligence Scale (Form L-M, Revised),[14] depending on which test was most suitable given the age of the child. The Bayley Scales may be administered up through 30 months of age; the Stanford-Binet test begins at 2 years of age. Both scales have a mean of 100 and a standard deviation of 16. For the purposes of this report the scores on both the Bayley Mental Scales and the Stanford-Binet examination were combined to yield the mean and standard deviation of the mental development/intelligence quotient score for the total group. Again, correction for gestational age was made only until 24 months, after which developmental scores were calculated according to chronologic age.

Results

Predictors of mortality. Table I presents the demographic and perinatal variables that were used to develop the prediction model. Pregnancy complications such as previous failed pregnancies, multiple births, incompetent cervix, prenatal infection, and placental abnormalities were prevalent, and infants were more likely to be delivered by cesarean section than by vaginal delivery.

Table I. Demographic and perinatal description of 80 inborn extremely low birth weight infants born between 1980 and 1985

Demographic background	
Maternal age (mean ± SD)	28 ± 5
Race (nonwhite) (%)	43.8
Social class (%)	
Major and minor business and skilled craftsman	71
Semiskilled laborer	9
Unskilled laborer	20
Birth data and perinatal risk factors	
Survival	21
Gravida (mean ± SD)	2.9 ± 1.7
> 1 Previous failed pregnancy (%)	17.5
Multiple birth (%)	25
Preeclampsia-hypertension (%)	17.5
Placenta previa (%)	3.8
Abruptio placenta (%)	3.8
Incompetent cervix (%)	6.3
Infection (%)	18.8
Type of delivery	
Vaginal (%)	49
Cesarean section (%)	51
Birth weight (gm, mean ± SD)	686 ± 82
Gestational age (wk, mean ± SD)	25.8 ± 1.8
Male sex (%)	46.3
Head circumference (cm, mean ± SD)	22.6 ± 1.4
Length (cm, mean ± SD)	31.8 ± 4.9
1 min Apgar score	3.2 ± 2.4
5 min Apgar score	5.1 ± 2.1
Initial pH (mean ± SD)	7.27 ± 0.13

Table II presents the estimates of the final stepwise logistic regression, their χ^2 values, and statistical significance levels, as well as a descriptive measure "partial R" of the net strength of the association of each predictor with mortality. As indicated in the table, only two of the variables, initial pH ($p \leq 0.029$) and 5-minute Apgar score ($p \leq 0.030$), are statistically significant at $p \leq 0.05$. Taken together, the joint predictive power of these two independent variables is 0.153 ($p < 0.001$). The negative signs of these variables indicate that relatively low scores on each predictor are associated with an increased probability of dying.

A more precise statement of these relationships can be made by comparing the odds of dying for infants with differing Apgar scores and pH values. For each unit increase in Apgar score, controlling for initial pH, the odds of dying decrease 1.38-fold or by 27%; for each 0.1 increase in pH, controlling for Apgar score, the odds of dying decrease 1.85-fold or by 46%.

A closely related way of expressing the relationships

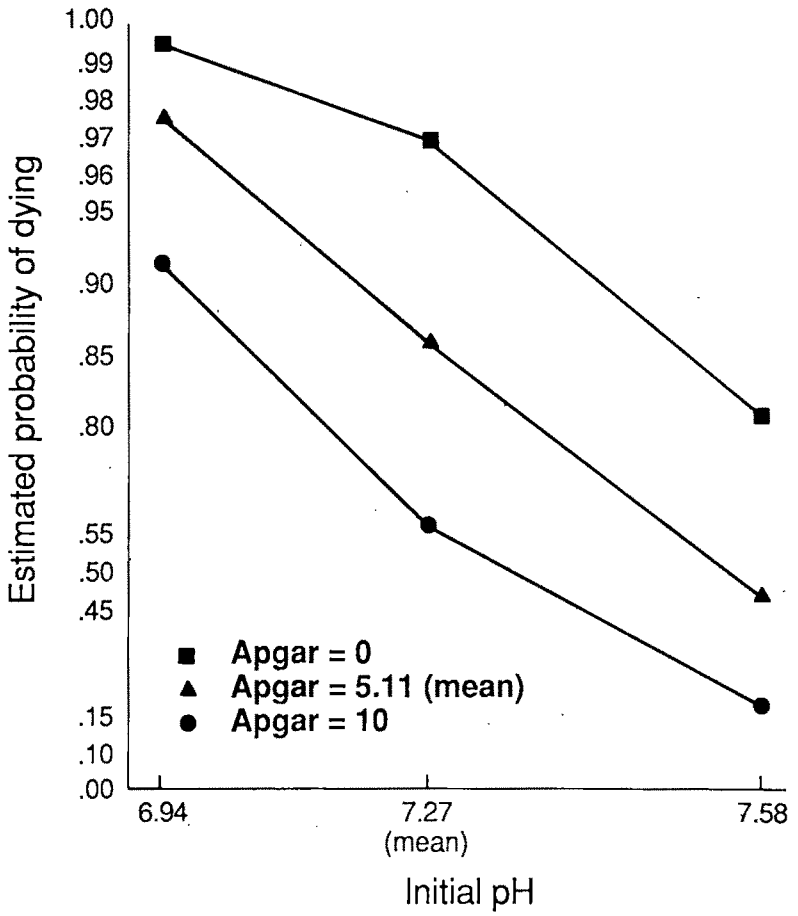


Fig. 1. Estimated probability of dying as a function of initial pH and 5-minute Apgar score.

among mortality, Apgar score, and initial pH is to graph the estimated probability of dying as a function of the latter two variables. As is indicated in Fig. 1, infants with low scores on both variables have substantially greater probabilities of dying than infants with high scores.

Long-term outcome. With regard to neurodevelopmental outcome, Table III shows that only 8 of 28 (28%) children could be considered completely normal (normal results of neurologic examination and mental ability scores ≥85) at the follow-up visit. Seventeen children (61%) had suspect results of neurologic examinations and/or mental development/intelligence quotient scores between 71 and 84. Three children (11%) had cerebral palsy and a mental development/intelligence quotient score of ≤70. Seventeen children had received or were receiving special services in the form of physical, occupational, and speech therapy or special education. Other residual problems included visual impairment (including retrolental fibroplasia, myopia, and strabismus) and attention-deficit hyperactivity disorder, accompanying other neurologic and developmental abnormalities, in 10 of 11 cases.

The children also had significantly lower percentiles in height and weight. Totals of 59% and 63% of children had heights and weights, respectively, below the 10th percentile, whereas only two children had either height or weight above the 50th percentile. Three children had microcephaly (head circumference below the 2nd percentile). Of these, two had mental development/intelligence quotient scores below 65.

Comment

Our analysis of 21 maternal and early neonatal variables revealed that only 5-minute Apgar score and initial pH were significant predictors of mortality in this cohort of infants. Although several previous studies[15-17] have examined the influence of perinatal factors on survival in the <1000 gm infant, we have confined our observations to those infants weighing between 500 and 799 gm. It is important to look at influences on mortality in this group apart from the 800 to 1000 or 1000 to 1500 gm infants to better define which obstetric or neonatal practices impact mortality in the extremely low birth weight infant.

Amon et al.[18] reported on the development of a prognostic model in 476 inborn infants with birth weights

Table II. Stepwise logistic regression model

Variable	*Regression coefficient*	χ^2	*p*	*Partial R*	R^2	*p*
1. Intercept	48.167	5.45	0.020			
2. Initial pH	−6.153	4.75	0.029	−0.182		
3. 5 min Apgar score	−0.319	4.73	0.030	−0.182	0.153	0.001

Table III. Long-term outcome of extremely low birth weight infants weighing <800 gm at birth (N = 28)

	Mental development/intelligence quotient score		
	≥85	*71-84*	*≤70*
Neurologic classification			
Normal (n = 16)	8	8	0
Suspect (n = 9)	5	2	2
Abnormal (n = 3)	0	0	3
Attention-deficit hyperactivity disorder		11	
Visual impairment		10	
Sensorineural hearing loss		1	
Rehabilitation, special education		17	
Weight < 10th percentile		17	
Height < 10th percentile		16	
Microcephaly		3	

≤1000 gm, born during 1980 to 1985. The most important variables that predicted survival were birth weight, 5-minute Apgar score, gestational age, cervical dilatation on admission, and race. Ales et al.,[19] using a similar model, analyzed all singleton pregnancies resulting in viable live-born infants weighing ≤1500 gm at birth. Here, birth weight and 5-minute Apgar score gave the greatest predictive accuracy. The definiton of viability was not specified in this study, and it is possible that many of the infants included in our analysis who died soon after delivery would have been eliminated from the study of Ales et al., thereby biasing their sample toward infants of larger birth weights and more advanced gestational age.

Our study confirmed the importance of the 5-minute Apgar score in predicting survival. Logistic regression analysis demonstrated that low Apgar scores were associated with an increased risk of dying. The Apgar score,[20] devised as a method to evaluate the need for resuscitation in the delivery room, provided an evaluation of the infant's general condition at birth and its ability to adapt to extrauterine life. It is a simple tool from which probability of death can be predicted, even in the extremely low birth weight infant.

Likewise, the initial pH obtained in the first hour of life served as an additional predictor of mortality. Infants in this study who were severely acidotic had a substantially increased risk of dying. The initial pH reflects the ability of the fetus to withstand the birth process without significant asphyxia and acidosis, as well as its ability to be adequately ventilated. In other words the physiologic maturity of the infant is what determines survival in this group of extremely low birth weight infants, and Apgar score and initial pH best reflected this developmental maturation.

Birth weight and gestational age in this group were no longer significant predictors because they no longer conferred additional meaningful maturity. Whether the Apgar score and initial pH can be significantly improved by obstetric and neonatal intervention and thereby lead to improved survival remains to be studied further.

With regard to the infants weighing <800 gm who survived, their outcome results are comparable to those of other centers reporting on infants born up through 1980.[3-11] This report is of a cohort of children admitted later, from 1980 to 1985, yet the 72% rate of overall handicap and the 9.8% mortality rate after neonatal intensive care unit discharge remain equally high. The years from 1980 onward represent a period in which there has been a concerted effort to improve the viability of the smallest infants, with concomitant interventions in perinatal management. Our results on outcome and those most recently published by Hack and Fanaroff[21] suggest that it may be difficult to effect improvements in morbidity among this group of smallest infants, despite refinements in neonatal intensive care.

Higher survival rates in infants of increasingly smaller birth weight signify that a greater number of infants will have neurologic and intellectual impairments that will require specialized intervention programs, both during the early years of life and throughout the school years. Of particular note here was the relatively high number of children with intelligence

quotients in the suspect category (between 71 and 84), indicating that the children will not be severely impaired in intellectual ability but that they will require special educational services. Studies of infants <1500 gm[22-25] have already shown a significantly higher prevalence of neurologic impairment, mental retardation, learning disabilities, sensory deficits, and behavior problems than is found in the normal population of children. When compared with the very low birth weight group (<1500 gm) the extremely low birth weight infants show about double the rate of neurodevelopmental problems.

We also demonstrated a shift toward lower percentiles in the heights and weights of the children who survived: >50% of children fell below the 10th percentile for both measures. Whether the growth of these children will approach a more normal distribution as they reach school age will be subject to further investigation. Studies reporting on the growth achievement at school age of infants ≤1500 gm at birth are conflicting, with some investigators reporting catch-up[26] and others not.[27]

Given the very-high-risk status of <800 gm infants, it is imperative that they be followed up carefully through school age. Looking toward the future, we can anticipate the need for expansion of resources for special education because of increasing numbers of children with special needs.

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The differential neonatal morbidity of the intrauterine growth retardation syndrome

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This is a prospective study of differential morbidity among subgroups of intrauterine growth retardation. Cases of intrauterine growth retardation (N = 3450) (≥37 weeks, <10th percentile birth weight for gestational age) were classified by their ponderal index (weight/length^3) in four subgroups using the 10th, 25th, and 90th percentiles of the Lubchenco's ponderal index-gestational age distribution. There were 432 cases (12.5%) with low ponderal index or disproportionate intrauterine growth retardation, 936 (27.1%) with intermediate ponderal index, 2030 (58.8%) with adequate ponderal index or proportionate intrauterine growth retardation, and 52 (1.5%) with high ponderal index. The low ponderal index group or disproportionate intrauterine growth retardation group had a statistically significant higher risk (between 1.6 and 12.5 times) for low 1- and 5-minute Apgar scores, aspiration syndrome, hypoglycemia, and perinatal asphyxia than the adequate ponderal index group. The low ponderal index group also had an increased risk (relative risk = 2.0 [95% confidence interval, 1.0 to 3.8]) for hospital stay of more than 1 week. These differences persist after a stratified analysis by birth weight and in a multiple logistic regression analysis. Similarly, higher neonatal morbidity is observed among infants with normal birth weights but with low ponderal index. These data provide further evidence of the heterogeneity of the intrauterine growth retardation syndrome and of the independent effect of body disproportion on neonatal morbidity, even among infants with normal birth weights. Because there are significant clinical implications attributed to the low ponderal index group, this subgroup should be identified as early as possible. (Am J Obstet Gynecol 1990;163:151-7.)

Key words: IUGR, ponderal index, neonatal morbidity

Infants with intrauterine growth retardation (IUGR) are at higher risk than their counterparts with normal birth weights for perinatal and infant morbidity and mortality as well as for congenital malformation.[1-3] It has been proposed that the group with IUGR is not homogenous and subclassifications with the weight/length ratio or ponderal index have been offered.[4-6]

These classifications differentiate at least two groups: those with IUGR and low ponderal index, wasted or disproportionate IUGR and those nonwasted, with proportionate growth retardation or adequate ponderal index.[7] The former group, associated with a shorter period of growth retardation, shows weight reduction but less marked reduction in length. The latter group has experienced fetal growth retardation in both weight and length.

In recent years several publications have shown that the cases of proportionate and disproportionate IUGR tend to have different epidemiologic characteristics,[8-9] as well as neonatal[10-11] and postneonatal growth and mental development patterns.[7, 12] Furthermore, a series of recent reports[13-17] after early suggestions by Scott and Usher[18] also demonstrated a differential neonatal morbidity of the subgroups of growth-retarded newborns. These reports show that the disproportionate (low ponderal index) IUGR group has higher neonatal morbidity, particularly hypoglycemia, perinatal asphyxia, hypothermia, and fetal distress and meconium aspiration than the proportionate IUGR group.

In this article we describe the neonatal morbidity found in a large cohort of infants with IUGR (as classified by their birth weight/length relationship) and the association between anthropometric characteristics of intrauterine growth retardation and early neonatal complications.

Material and methods

This was a prospective follow-up study of 16,850 pregnant women who had their first prenatal visit be-

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Table I. Anthropometric characteristics of the IUGR population by ponderal index levels

Total IUGR population	*LPI (n = 432)*	*IPI (n = 936)*	*API (n = 2030)*	*HPI (n = 52)*	*p value*
Birth weight (gm)	2444 ± 303	2575 ± 234	2627 ± 205	2642 ± 228	0.001
Length (cm)	48.7 ± 1.9	47.8 ± 1.5	46.4 ± 1.4	40.7 ± 3.9	0.001
Head circumference (cm)	32.7 ± 1.6	32.6 ± 1.4	32.8 ± 1.3	32.9 ± 1.1	NS
Gestational age (wk)	39.4 ± 0.9	39.4 ± 0.8	39.3 ± 0.8	39.3 ± 0.8	NS
Ponderal index (gm/cm^3)	2.1 ± 0.1	2.3 ± 0.05	2.6 ± 0.1	3.9 ± 1.1	*

Data represent mean ± SD.
LPI, Low ponderal index; *IPI,* intermediate ponderal index; *API,* adequate ponderal index; *HPI,* high ponderal index.
*Differences obtained by definition of the groups. No further statistical testing required.

tween April 1984 and January 1986 at the antenatal clinic of the Gynecology and Obstetrics Hospital of the Guatemalan Social Security Institute, Guatemala. A detailed description of this population and its health care characteristics has been published elsewhere.[19, 20] This is an urban, predominantly working-class population and women eligible to receive Social Security health benefits include those women who are formally employed and wives of employed men.

The Gynecology and Obstetrics Hospital is a tertiary level 230-bed hospital where all deliveries of infants of eligible women who use the Social Security system occur. The hospital is staffed with obstetrics-gynecology residents and trained obstetricians for prenatal and delivery care. All cesarean deliveries and high-risk deliveries are attended by pediatric-neonatology residents.

Birth weight, length, head circumference, and gestational age by physical examination were obtained immediately after birth from all newborns by a team of specifically trained neonatal nurses. Birth length measurements were taken on a standard measuring table as previously described.[10] Gestational age by physical examination was calculated with a simplified version of the Dubowitz method.[21]

A standardization process was completed before initiation of data collection and a data quality control system was implemented during the study period for all variables and anthropometric measurements studied. The newborn information had excellent reliability and very low measurement errors.[22, 23]

All clinical assessments of neonatal morbidity were determined by a senior neonatologist and recorded in the neonatal intensive care unit precoded summary form. A trained research clerk abstracted the data daily and completed the study data collection form in consultation with a senior neonatologist (R. C.) and the study field director (F. B.). The nurses and neonatologists were only aware that an epidemiologic study was being conducted, but they were not informed of the specific hypotheses being tested.

Of the 16,850 women enrolled in the study, 362 were excluded because they either did not have complete data, or one of the newborn anthropometric values was >3 SDs for this population. There were 16,488 singleton live births with complete information on anthropometric characteristics and gestational age at delivery. Six hundred ten (3.7%) births were preterm (<37 weeks) and are not considered in this analysis. The term population (≥37 weeks) was divided as infants with normal birth weights (N = 12,428) or term intrauterine growth retarded (N = 3450, 21%) if above or below the 10th percentile of a sex-specific birth weight for gestational age distribution from a well-nourished population.[24] Infants were further classified into four groups by their ponderal index values ($weight/length^3$)[6] according to the 10th, 25th, or 90th percentile of a ponderal index for gestational age distribution.[25] These groups constitute the subjects of this report.

Neonatal morbidity identified up until discharge from the hospital or the neonatal intensive care unit was the dependent variable. The morbidity information available in the precoded summary form included: *1- and 5-minute Apgar scores* determined by either a neonatal nurse or a pediatric resident; *length of hospital stay* in days; *perinatal distress* as an overall clinical evaluation based on at least one of the following: abnormal fetal heart rates, Apgar score ≤6 at 5 minutes, more than a trace of meconium-stained amniotic fluid at the time of membrane rupture in a nonbreech presentation, or newborn acidosis; *hypoglycemia* (≤35 mg/dl within 72 hours after birth) among those infants with IUGR admitted to the neonatal intensive care unit (N = 221); *aspiration syndrome* as diagnosed by the presence of meconium in the trachea while suctioning the airway after birth; clinical manifestations of aspiration (e.g., respiratory distress) and chest x-ray films; *hyperbilirubinemia* (>15 mg/dl), and any *neonatal infection,* including meningitis, by clinical diagnosis and laboratory confirmation, reported as present/absent, age at diagnosis, localization and, when possible, type. In addition, events related to labor and delivery such as rupture of membranes; duration of labor; use of oxytocin, anesthesia, or other drugs; type of delivery; and amniotic fluid characteristics were also recorded.

The incidence of morbidity for the ponderal index subgroups was calculated and are presented for the total population and stratified by birth weight. Adjusted odds ratios were obtained with logistic regres-

Table II. Incidence of neonatal morbidity for the IUGR subgroups

	Ponderal index level			*p Value for linear trend**
	LPI (n = 432)	*IPI (n = 936)*	*PI (n = 2030)*	
Apgar score				
1 min ≤3	14.60†	8.90†	5.70	‡
5 min ≤6	3.16†	1.41	1.05	‡
Aspiration syndrome	2.79†	0.75†	0.20	‡
Hypoglycemia	2.08†	0.64	0.35	‡
Perinatal distress§	3.25†	1.18	0.60	‡
Hyperbilirubinemia	3.01†	1.39	1.13	NS
Infections	1.62†	0.96	0.40	‡
Age at hospital discharge (>7 days)	5.62†	2.25†	1.14	‡

LPI, Low ponderal index; *IPI,* intermediate ponderal index; *API,* adequate ponderal index.

*χ^2 for trend.

†$p < 0.05$, in comparison with IUGR-API.

‡$p < 0.01$

§Perinatal distress: Overall clinical evaluation based on at least one of the following: abnormal fetal heart rate patterns (auscultation), low Apgar score, meconium-stained amniotic fluid, and neonatal acidosis.

sion analysis[26] for each morbidity indicator with the IUGR/adequate ponderal index group as the reference.

Birth weight, length, gestational age, and ponderal index expressed in a continuous form were further included as independent variables in a multiple regression logistic[26] model aimed to predict each of the neonatal morbidity indicators.

The a priori hypothesis that infants with intrauterine growth retardation and low ponderal index (disproportionate IUGR), independently of birth weight, have higher neonatal morbidity than those with adequate ponderal index (proportionate IUGR) was tested.

Results

There were 432 (12.5%) infants with low ponderal index (IUGR-LPI); 936 (27.1%) intermediate ponderal index (IUGR-IPI); 2030 (58.8%) adequate ponderal index (IUGR-API); and 52 (1.5%) high ponderal index (IUGR-HPI). Among the normal birth weight term group (n = 12428) 1.06% were of low ponderal index, 9.8% of intermediate, 82.0% of adequate ponderal index, and 7.1% of high ponderal index.

The mean birth weight of the IUGR-LPI group was lower than the other three groups with IUGR; however, the IUGR-LPI group was taller than the other groups, whereas the IUGR-HPI group was significantly shorter ($p < 0.01$). The IUGR-HPI group had a mean length of 40.8 ± 4.0 cm (Table I). It included nine infants who were less than 36 cm, three of whom had congenital malformations. Given the small sample size and the abnormal number of congenital malformations, this group will be excluded from the morbidity analysis.

First stage of labor lasting more than 12 hours was more common among the IUGR-LPI group (15% versus 11%) ($p < 0.02$) and this group also had higher rates of forceps or vacuum deliveries (3.3%) than the IUGR-API group (1.6%) ($p < 0.01$). Elective cesarean section were higher in the IUGR-API group (3.8%) than the IUGR-LPI group (1.4%) ($p < 0.05$). The low ponderal index-IUGR group had higher incidence of meconium-stained amniotic fluid (18.9%) than the intermediate ponderal index (14.4%) and the adequate ponderal index groups (9.5%) ($p < 0.01$).

Table II presents the incidence of neonatal morbidity for the IUGR subgroups. For all morbidity indicators, rates were highest for the low ponderal index group and lowest for the group with API-IUGR. There is also a statistically significant trend in rates of morbidity from the LPI-IUGR group to the API-IUGR group.

To explore the independent effect of low birth weight and ponderal index, we further stratified the IUGR population by birth weight level (≤2500 gm and >2500 gm) and compared within each stratum the LPI-IUGR with the API-IUGR subgroup.

There were 213 LPI-IUGR and 489 API-IUGR infants among those with birth weights ≤2500 gm. The mean birth weights were 2214 (±264) gm vs 2338 (±152) gm and the mean lengths were 47.5 (±0.4) cm versus 44.7 (±0.8) cm for the groups with low ponderal index and adequate ponderal index, respectively. There were 219 LPI-IUGR and 1541 API-IUGR in the group with birth weights >2500 gm. The mean birth weights were 2666 (±114) gm versus 2718 (±114) gm and the mean lengths were 49.8 (±1.1) cm versus 46.9 (±1.0) cm for the groups with low ponderal index and adequate ponderal index, respectively.

In addition, the population with normal birth weight (>10th percentile birth weight for gestational age) was also classified by ponderal index level according to the same reference standard.[25] There were 132 infants with

Table III. Incidence of neonatal morbidity (percent) for infants with IUGR and normal birth weights classified by their ponderal index levels

	IUGR				*Normal birth weight*	
	≤2500 gm		*>2500 gm*			
	LPI (n = 213)	*API (n = 489)*	*LPI (n = 219)*	*API (n = 1541)*	*LPI (n = 132)*	*API (n = 10,192)*
Apgar score						
1 min ≤3	8.4	3.3*	3.4	0.9†	8.8	0.9*
5 min ≤6	3.9	2.1 (NS)	2.4	0.7‡	8.0	0.5*
Aspiration syndrome	3.3	0.6‡	2.3	0.1*	5.3	0.4*
Hypoglycemia	2.8	0.8‡	1.4	0.2†	2.2	0.1*
Perinatal distress§	4.7	1.4‡	1.8	0.3‡	8.3	0.5*
Hyperbilirubinemia	5.2	2.7 (NS)	0.9	0.6 (NS)	0.8	0.4 (NS)
Infections	1.9	1.2 (NS)	1.4	0.1†	2.3	0.5*
Age at hospital discharge (>7 days)	9.5	2.1*	1.8	0.8 (NS)	3.1	0.8*
Congenital malformations‖	4.7	3.9 (NS)	0.5	0.6 (NS)	0.8	0.6 (NS)

Sample size is indicated in parentheses.

Normal birth weight >10th percentile birth weight for gestational age.[24]

*$p < 0.001$, as compared with the corresponding group with low ponderal index.

†$p < 0.01$, as compared with the corresponding group with low ponderal index.

‡$p < 0.05$, as compared with the corresponding group with low ponderal index.

§Perinatal distress: Overall clinical evaluation based on at least one of the following: abnormal fetal heart rate patterns (auscultation), low Apgar score, meconium-stained amniotic fluid, and neonatal acidosis.

‖Up to hospital discharge.

low ponderal index and normal birth weight; 10,192 infants with adequate ponderal index and birth weight above the 10th percentile of birth weight for gestational age. The mean birth weights were 3035 (±255) and 3268 (±313) gm and mean lengths were 51.8 (±1.6) and 49.3 (±1.5) cm for the groups with low ponderal index and normal birth weight and adequate ponderal index and normal birth weight, respectively. The mean gestational ages were 39.3 (0.8) weeks for the group with low ponderal index and normal birth weight and 39.3 (±0.7) weeks for the group with adequate ponderal index and normal birth weight.

As seen in Table III, the low ponderal index groups (either IUGR or normal birth weight) have, in the three comparisons, higher neonatal morbidity than the groups with adequate ponderal index. Interestingly, the morbidity ratio between the low ponderal index and adequate ponderal index subgroups increases with increasing birth weight. For example, the group with LPI-IUGR ≤2500 gm has 2.5 times higher risk for 1-minute Apgar scores ≤3 than its API-IUGR counterpart; the LPI-IUGR >2500 gm group has 3.8 times more risk of low Apgar score than the group with API-IUGR >2500 g. Finally, the low ponderal index-normal birth weight group has 9.8 times higher risk of low Apgar score than the group with adequate ponderal index-normal birth weight (Table III).

Table III also presents data on the incidence of major congenital malformations diagnosed by neonatologists before discharge from the hospital. There were 106 infants diagnosed in these subgroups with an overall incidence of 0.8%. No differences were observed between infants with low ponderal index and adequate ponderal index at any level of birth weight.

Table IV presents birth weight adjusted odds ratios for the morbidity variables. These odds ratios represent the increased risk over the IUGR-API group and are adjusted by birth weight, which is known to be associated with neonatal morbidity among infants with IUGR.[27] This adjustment allows for the evaluation of the independent effect of the IUGR anthropometric characteristics on neonatal morbidity. Again, the IUGR-LPI group experienced higher risks for morbidity with the exception of hyperbilirubinemia, as compared with the IUGR-API group (low 5-minute Apgar score, hypoglycemia and infection did not reach $p < 0.05$ level). The IUGR-IPI group had values in between. An inverse trend clearly emerges in these tables between neonatal morbidity and ponderal index.

Finally, analyses were also performed for the newborn anthropometric measurements expressed as continuous variables. High negative correlation coefficients were observed between ponderal index and infant length ($R = -0.67$; $p < 0.001$). Thus, in the logistic regression analysis, only ponderal index, birth weight, and gestational age are included as independent variables. Each morbidity indicator is used as a dependent variable.

Table IV. Risk of neonatal morbidity for the IUGR subgroups (adjusted by birth weight*)

	IUGR subgroups			
	Low ponderal index (N-432)		*Intermediate ponderal index (N-936)*	
	Odds ratio	*95% CI*	*Odds ratio*	*95% CI*
Apgar score				
1 min ≤3	2.0	1.1 – 3.7†	1.0	0.5 – 1.8
5 min ≤6	1.6	0.7 – 3.5	1.1	0.6 – 2.3
Aspiration syndrome	12.5	3.9 – 40.8	3.7	1.1 – 12.6
Hypoglycemia	2.7	0.9 – 8.3	1.5	0.5 – 4.5
Perinatal distress‡	3.2	1.4 – 7.5	1.7	0.7 – 3.8
Hyperbilirubinemia	1.0	0.4 – 2.2	0.9	0.5 – 1.8
Infections	2.5	0.8 – 7.5	2.1	0.8 – 5.6
Age at hospital discharge (>7 days)	2.0	1.0 – 3.8	1.5	0.8 – 2.7

*Logistic regression analysis.

†All odds ratios and 95% confidence intervals (95% CI) are calculated with the IUGR-API group ($N = 2030$) as a reference population. They should be interpreted as increased risk over the IUGR-API group (odds ratio = 1.00).

‡Perinatal distress: Overall clinical evaluation based on at least one of the following: abnormal fetal heart rate patterns (auscultation), low Apgar score, meconium-stained amniotic fluid, and neonatal acidosis.

Table V. Logistic regression analysis of the effect of birth weight, gestational age and ponderal index expressed as continuous variables on neonatal morbidity

*Neonatal morbidity** *(dependent variable)*	*Ponderal index (weight/cm³)*	*Birth weight (gm)*	*Gestational age (wk)*	*n*
Hyperbilirubinemia	−0.09 (0.5)†	−0.003 (0.0005)‡	−0.15 (0.2)	3162
Aspiration syndrome	−2.14 (0.8)‡	−0.002 (0.0007)§	1.18 (0.2)‡	3162
Perinatal distress	−1.06 (0.7)‖	−0.003 (0.0006)‡	0.39 (0.2)§	3162
Hypoglycemia	−1.01 (0.9)	−0.003 (0.0007)‡	0.06 (0.2)	3162
Low Apgar score at 1 min ≤6	−0.44 (0.24)‖	−0.002 (0.0002)‡	0.35 (0.1)‡	3117
Mecomium-stained amniotic fluid	−0.98 (0.24)‡	−0.0008 (0.0002)‡	0.79 (0.1)‡	3159
Infections	−0.93 (0.95)	−0.001 (0.0009)‖	−0.58 (0.3)§	3162

Perinatal distress: Overall clinical evaluation based on at least one of the following: abnormal fetal heart rate patterns (auscultation), low Apgar score, meconium-stained amniotic fluid, and neonatal acidosis.

*Presence or absence of the characteristics.

†Adjusted regression coefficient with standard error in parentheses; logistic regression analysis.

‡$p < 0.01$.

§$p < 0.05$

‖$p < 0.10$

As can be observed in Table V, ponderal index was negatively associated with all indicators of neonatal morbidity, reaching statistically significant levels, after adjusting by birth weight and gestational age, in all of the morbidity indicators, with the exception of hyperbilirubinemia, hypoglycemia, and infections. As expected, birth weight was also negatively and significantly associated with all indicators of neonatal morbidity. To summarize, the ponderal index level, independently of birth weight and gestational age, is negatively associated with neonatal morbidity among term infants with intrauterine growth retardation.

Conversely, gestational age in this population of term (≥37 weeks) infants with intrauterine growth retardation is positively associated with all neonatal morbidity indicators except hyperbilirubinemia and infections (Table V).

Comment

We have presented evidence from a large prospective study that the level of disproportionality (weight/length ratio) among infants with IUGR and normal birth weight is an independent predictor of neonatal morbidity, after adjusting by birth weight. This evidence is observed when ponderal index is expressed by percentile level groups (low to adequate) or as a continuous variable: the lower the ponderal index, the higher the neonatal morbidity.

The IUGR-API or proportioned IUGR group could include a number of normal, yet small infants, representing the lowest end of a normal distribution of fetal growth. This could partially explain the lower morbidity observed in this subgroup as compared with the LPI-IUGR groups. Although this may be the case among well-nourished populations that have reached their full growth potential, it is unlikely to represent a large proportion of the group with intrauterine growth retardation in underprivileged populations.[9] Infants with intrauterine growth retardation-adequate ponderal index from both developed and developing populations score lower in developmental tests compared with infants IUGR-LPI and normal birth weights.[7, 12] This would not be expected if these infants were only genetically smaller.

Nevertheless, data for Table III also suggests that the API-IUGR group weighing >2500 gm may include a number of infants that are genetically small and not growth retarded. This group had similar early neonatal morbidity to the adequate ponderal index-normal birth weight group. Both figures are considerably lower than those of the group with adequate ponderal index intrauterine growth retardation with birth weights <2500 gm.

The heterogeneity of fetal malnutrition is similar to the subgroups described among malnourished children (wasted-stunted) and contributes further to support the biologic similarities between intrauterine and extrauterine malnutrition.

Preliminary studies, all based on small sample sizes, support the differential morbidity pattern reported here for the IUGR subgroups. The IUGR-LPI group experienced higher rates of meconium-stained amniotic fluid, meconium aspiration,[13] fetal distress,[17, 18] perinatal asphyxia and low Apgar score,[14-17] and as also observed here, increased risk for intrapartum interventions.[17]

Infants with disproportionate IUGR also have higher incidence of hypoglycemia than the IUGR-API group, confirming previous reports.[13-16] These infants, with acute malnutrition or wasting, similar to children with an acute caloric restriction during childhood, have been shown to have insufficient glycogen liver stores[4] and diminished subcutaneous fat reserves.[27, 28] This is aggravated by their higher rate of perinatal distress resulting in a reduced gluconeogenic response to hypoglycemia. In contrast, infants with proportionate IUGR, similar to stunted children, tend to have adequate glucose homeostasis.

The increased morbidity of the disproportionate growth-retarded infants is in agreement with the higher neonatal and perinatal mortality that has been observed in this subgroup.[29, 30] For example, in two populations from developing countries, infants with disproportionate IUGR had between 2.0 and 2.8 times higher risk of early neonatal mortality.[29] Similarly, asymmetrically formed infants from Norway had 4.6 times greater perinatal mortality than those with appropriate weight and length.[30]

We have provided evidence of the heterogeneity of the IUGR population, suggesting that the ponderal index effect may be present among infants with normal birth weight. It should be remembered, however, that the morbidity patterns of IUGR are different at different postneonatal ages. The group with disproportionate IUGR-LPI has higher neonatal morbidity, as was demonstrated here, whereas the group with proporionate IUGR-API experiences higher rates of abnormal postneonatal growth and development.[7, 10, 12]

In this analysis no differential effect was observed in relation to congenital malformations by ponderal index level. The effect of IUGR on congenital malformations is the subject of a more detailed study currently being conducted.

Finally, the analysis presented in Table V shows that neonatal morbidity of term infants with intrauterine growth retardation (≥37 weeks) is positively associated with gestational age: neonatal morbidity is higher the longer the infant remains in utero after 37 weeks. These data support the recommendation of delivering infants with IUGR when they reach pulmonary maturity.[31] This recommendation appears to be more important among infants with disproportionate IUGR who are at higher morbidity risks.

This study lends support to the importance of early antenatal identification of IUGR and it subgroups with the use, for example, of ultrasonographically determined anthropometric ratios.[17, 32] This could provide additional information for a more adequate perinatal management including, if necessary, the early delivery of infants with LPI-IUGR.

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Growth of linear parameters in trisomy 18 fetuses

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Linear growth in fetuses with trisomy 18 has not been systematically described. We studied the relationship between long-bone, crown-rump, and foot length and gestational age in 17 postmortem fetal specimens with this syndrome. Long-bone and crown-rump lengths were compared with normal regression lines and foot length was compared with gestational age determined on the basis of menstrual dates. Correlation between foot length and menstrual dates was weak in trisomy 18. Gestational age predicted by crown-rump length was significantly lower than gestational age by menstrual dates. All long bones were significantly shortened and fell below normal regression lines for gestational age. The fetal femur/foot length ratio was reduced. Thus no endogenous measure of gestational age appears to exist in this aneuploidy, forcing reliance on menstrual dates. The observed pattern of growth alterations will likely preclude the development of a gestational age–dependent biometric screen for the prenatal detection of this syndrome. (Am J Obstet Gynecol 1990;163:158-61.)

Key words: Trisomy 18, linear growth, bone length

Trisomy 18 is the second most common autosomal trisomy in man with an estimated incidence of 0.3/1000 live births.[1] Morphologic and pathologic findings of this syndrome in newborns have been extensively described,[2] but little is known about growth of affected fetuses. Intrauterine growth retardation and severe postnatal failure to thrive are thought to be common.[2, 3] Recently, altered growth of the limbs has received considerable attention as a potential sonographic screen for Down syndrome.[4, 5] Similar information on limb length in fetuses with trisomy 18 is not available. We report on linear growth of the crown-rump length, the foot, and the long bones of the upper and lower extremities in postmortem second- and third-trimester fetuses with this syndrome.

Material and methods

The methods for collection and postmortem examination of fetal specimens in the Central Laboratory for Human Embryology have been previously published.[6]

Control fetuses were selected at random from a group of fetal specimens that resulted from either spontaneous or elective abortions. The karyotype was unavailable on these fetuses, but a detailed fetal autopsy did not disclose abnormalities. The prevalence of aneuploidy should be quite low in this group.[7]

Long-bone measurements were taken from a roentgenogram of the fetal limbs or were obtained by direct measurement after digestion of soft tissues in 5% or 10% potassium hydroxide. We have previously shown close correlation of roentgenogram and digestion techniques with minimal distortion.[8] Measurements obtained by digestion were converted to their roentgenogram equivalent by way of a regression equation. The control specimens were dated by foot length, which has been shown to be an accurate measure of gestational age in normal fetuses.[9] Long-bone lengths were plotted against gestational age by foot length, and appropriate linear regression equations were calculated. The normal bone lengths predicted by our regression equations fell well within the normal ranges of published long-bone growth curves as measured by ultrasonography.[10] The second-trimester control specimens were grouped by gestational week, and means and SDs were calculated for length of the long bones. These techniques with the applicable regression equations and normal ranges have been previously described in detail.[8]

The records of the Central Laboratory for Human Embryology were reviewed and nine second- and eight third-trimester fetuses with the trisomy 18 karyotype were identified. Limited information was available on one additional specimen that had been examined at an outside hospital. Some fetuses were studied immediately after termination of pregnancy, whereas others

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Table I. Crown-rump and foot length versus gestational age

*Gestational age**	*Crown-rump length† (mm)*	*GA by CRL‡*	*GA by FL§*	*GA‖*
113	132	112 ± 9	16.7	18.1
118	127	111 ± 9	18.1	18.9
118	—	—	15.7	18.9
123	132	112 ± 9	17.4	19.6
123	156	129 ± 9	18.8	19.6
126	120	106 ± 9	17.7	20.0
130	120	106 ± 9	18.8	20.5
131	131	112 ± 9	16.4	20.6
136	155	128 ± 9	20.5	21.4
139	157	130 ± 9	19.5	21.9
188	148	122 ± 9	18.4	28.9
189	220	167 ± 9	25.6	29.0
200	245	¶	26.7	30.6
200	228	¶	26.4	30.6
210	—	—	28.3	32.0
230	190	149 ± 9	23.4	34.9
253	224	170 ± 9	28.3	38.0
257	190	149 ± 9	—	38.9

*In postconception days by last menstrual period.
†Sitting crown-rump length in millimeters.
‡Gestational age by crown-rump length expressed as mean in days ± 95% prediction interval.[17]
§Gestational age in weeks by foot length based on Streeter et al.[15]
‖Gestational age in weeks by last menstrual period.
¶Crown-rump length exceeds normal curve.

had been stored in 10% formalin since autopsy. Long-bone measurements were obtained by the roentgenogram technqiue.

Gestational age by last menstrual period was compared with gestational age according to the fetal foot length. The individual bone lengths of trisomic fetuses were compared with the normal regression lines for that bone. Whereas the gestational age in the 174 control fetuses had been assigned by foot length, menstrual dates were used to plot the trisomy 18 specimens. For the second-trimester trisomic specimens, bone lengths were also compared with the normal means for each gestational week. Too few normal third-trimester specimens were available to allow similar comparisons for specimens at older gestational ages.

Gestational age predicted by sitting crown-rump length according to the normal regression line in use at the Central Laboratory for Human Embryology[11] was compared with the gestational age of the specimen according to the last menstrual period. Finally, the femur/foot length ratios were calculated for the trisomic specimens.

Statistical analysis was by way of the one-sample or two-tailed paired Student *t* test for parametric data and the sign test for nonparametric data.

Results

Fetal foot length had been measured in 16 of our 17 specimens and the additional specimen from an outside institution. In the trisomic fetuses, a relatively poor correlation ($R^2 = 0.52$) was found for foot length and menstrual dates with gestational age by dates universally exceeding gestational age calculated from the fetal foot length (Table I). This difference was statistically significant ($p < 0.02$, Student paired *t* test). Therefore all trisomic specimens were dated according to the last menstrual period.

After 18 weeks' gestation the gestational age predicted by the sitting crown-rump length of the trisomic specimens was consistently less than the gestational age calculated from the last menstrual period (sign test; $p = 0.0012$; Table I).

All long-bone lengths in fetuses with trisomy 18 fell below the normal regression line for that bone. This observation is highly statistically significant (sign test; $p < 0.001$ for the lower extremity long bones, $p < 0.005$ for the upper extremity long bones). When compared with expected bone lengths calculated from the regression equations, upper and lower extremity bones of fetuses with trisomy 18 were significantly shorter (Student paired *t* test; $p < 0.002$; Table II).

In the nine second-trimester fetuses with trisomy 18, the long bones of the lower extremity were generally >2 SDs shorter than the normal mean for gestational age. Only two of nine femur lengths did not adhere to this pattern. In the upper extremity, long-bone shortening was less consistent with two of eight humeri, two of seven ulnas, and three of seven radii, measuring

Table II. Trisomy 18 long-bone lengths

Gestational age*	Femur		Tibia		Fibula		Humerus		Ulna		Radius	
	Obs	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*
18.1	22.00	24.90	19.00	21.77	18.00	21.31	—	—	—	—	—	—
18.9	23.00	27.20	20.00	23.39	18.00	23.06	23.40	26.60	—	—	—	—
19.6	26.00	29.20	21.00	25.60	20.00	24.60	25.50	28.48	21.00	25.71	18.00	23.00
19.6	28.00	29.20	24.00	25.60	23.00	24.60	28.00	28.48	25.00	25.71	22.00	23.00
20.0	25.65	30.36	20.89	26.62	19.12	25.48	24.97	29.55	21.02	26.72	20.83	23.85
20.5	29.00	31.80	24.00	27.89	22.00	26.58	28.00	30.89	25.00	27.98	22.00	24.92
20.6	21.50	32.07	18.00	28.15	17.50	26.80	21.00	31.16	19.50	28.23	17.00	25.14
21.4	31.00	34.37	27.00	30.19	25.00	28.55	30.00	33.30	28.00	30.25	26.00	26.85
21.9	30.00	35.88	25.30	31.46	23.50	29.65	30.00	34.64	26.00	31.51	23.30	27.99
28.9	29.00	55.87	25.00	49.31	—	—	—	—	—	—	—	—
29.0	47.00	56.15	39.00	49.57	35.00	45.24	—	—	—	—	—	—
30.6	45.00	60.67	38.00	53.65	36.00	48.75	41.00	57.95	36.00	53.46	32.00	46.57
30.6	49.00	60.67	41.00	53.65	39.00	48.75	43.00	57.95	41.00	53.46	36.50	46.57
32.0	48.00	64.77	41.00	57.21	38.25	51.82	42.00	61.70	40.50	56.99	37.00	49.56
34.9	46.00	73.10	37.50	64.61	35.00	58.19	—	—	—	—	—	—
38.1	67.50	82.27	57.00	72.77	53.50	65.22	59.5	78.05	53.00	72.38	47.50	62.64
38.9	41.00	84.54	34.00	74.81	—	—	—	—	—	—	—	—

Obs, Observed bone length in millimeters; *Exp*, expected length in millimeters calculated from regression equations according to FitzSimmons et al.[8]

*Expressed in menstrual weeks.

Table III. Second-trimester long-bone lengths, normal ranges

Cases (wk)	Controls (wk)	Femur (mm)	Tibia (mm)	Fibula (mm)	Humerus (mm)	Ulna (mm)	Radius (mm)
	18	26.13 ± 1.50	22.96 ± 1.56	21.95 ± 1.45	26.26 ± 1.33		
18.1		22.00	19.00	18.00			
18.9		23.00	20.00	18.00	23.40		
	19	29.47 ± 1.52	25.52 ± 1.16	24.40 ± 0.96	29.13 ± 1.29	25.97 ± 1.17	24.05 ± 1.19
19.6		26.00	21.00	20.00	25.50	21.00	18.00
19.6		28.00	24.00	23.00	28.00	25.00	22.00
	20	31.66 ± 3.18	27.95 ± 3.09	26.59 ± 2.82	31.56 ± 4.26	28.16 ± 3.58	27.38 ± 5.03
20.0		25.65	20.89	19.12	24.97	21.02	20.83
20.5		29.00	24.00	22.00	28.00	25.00	22.00
20.6		21.50	18.00	17.50	21.00	19.50	17.00
	21	35.13 ± 2.38	30.46 ± 1.65	29.45 ± 1.50	34.31 ± 1.77	31.72 ± 1.09	27.18 ± 4.64
21.4		31.00	27.00	25.00	30.00	28.00	26.00
21.9		30.00	25.30	23.50	30.00	26.00	23.30

Bone lengths are expressed in millimeters as mean ± 2 SD.

within 2 SDs of the normal mean for gestational age (Table III).

The mean femur/foot length ratio for the trisomic specimens was 0.714 ± 0.076 (range, 0.604 to 0.904), which falls significantly below the accepted normal range of 0.99 ± 0.06[12] during the second and third trimester (one-sample t test, $p < 0.001$).

Comment

Growth retardation is a recognized component of the trisomy 18 syndrome. Birth weights of affected fetuses and term or near-term neonates almost universally fall well below population means.[2, 3, 13, 14] Until recently, reduced growth of the crown-rump length and shortening of the long bones had been noted only in case reports.[15, 16] Lynch and Berkowitz[17] have now confirmed the early growth delay in this syndrome by sonographically showing crown-rump lengths that are smaller than expected in five first-trimester fetuses with trisomy 18. To date, however, second-and third-trimester linear growth in this second most common autosomal trisomy had not been studied systematically.

Our findings indicate that the upper and lower extremities in fetuses with trisomy 18 are significantly shortened. This deficiency in growth begins before week 18 of gestation and growth remains subnormal through the remainder of fetal development. Our data suggest that the lower extremity is more consistently affected than the upper limb. This finding is in contrast to our previous report of disproportionately reduced

growth of the upper extremity in Down syndrome.[8] In trisomy 18 growth of the lower limb thus appears to be less closely channelled than upper extremity development, which might also explain the lower extremity limb reduction abnormalities that have been noted by other authors.[18] In addition, we confirm the truncal growth delay noted by Lynch and Berkowitz, although in our series this did not become a consistent finding until after 18 weeks' gestation.

Fetal foot length is generally thought to be a reliable indicator of gestational age, making reliance on subjective recall of the last menstrual period unnecessary and adding valuable confirmatory information when other parameters do not accurately predict gestational age.[19] However, in trisomy 18, we have shown a poor correlation between foot length and gestational age by menstrual dates. This indicates that the profound growth deficiency that affects the lower extremity also affects growth of the foot, although growth of the foot appears to be better preserved than growth of the femur as suggested by the abnormally low femur/foot length ratios. A similar abnormality has been observed for the biparietal diameter/femur length ratio.[20] Because biparietal diameter and abdominal circumference also have reduced rates of growth in this syndrome,[21] our findings of universally slowed linear growth in fetuses with trisomy 18 supports the concept of an overall reduced potential for growth in this aneuploid condition.

The fact that the fetus with trisomy 18 lacks a reliable endogenous measure of gestational age is of clinical significance because a dependable sonographic screen would be highly desirable for a condition that has such serious implications for perinatal management and pregnancy outcome.[15] The utility and predictive value of such a sonographic screen for Down syndrome remain controversial.[5, 22] Unfortunately the data suggest that the symmetry of the observed growth deficiency, and the apparent lack of an endogenous predictor of gestational age in trisomy 18 will likely preclude the development of a gestational age–dependent biometric screen such as the "observed/expected" ratios that have been proposed for Down syndrome screening. Whether a parameter that is independent of gestational age, such as the femur/foot length or biparietal diameter/femur length ratio, will prove to be sufficiently specific to be of diagnostic use deserves further prospective study.

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Recurrent adverse pregnancy outcome and antiphospholipid antibodies

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Antiphospholipid antibodies, which include lupus-like anticoagulant and anticardiolipin antibody, have been linked to a number of adverse pregnancy outcomes, although their exact pathogenic mechanisms remain poorly defined. The relative risk of complications such as intrauterine growth retardation, spontaneous abortions, and stillbirth in patients with antiphospholipid antibodies also remains undetermined. Heightened attention has been focused on the association, leading to investigations into the pathogenesis. Uncontrolled studies have also explored therapeutic regimens such as aspirin, steroids, and heparin, and clinical trials have used various treatment protocols. Although knowledge into the association of antiphospholipid antibodies and recurrent adverse pregnancy outcome is limited and continues to evolve, this association provides new insights into the disease and offers promise for pharmacologic prophylaxis. In this article, current concepts on pathogenesis, diagnosis, and therapy are reviewed and recommendations are made for clinical care of these patients. (Am J Obstet Gynecol 1990;163:162-9.)

Key words: Antiphospholipid antibodies, spontaneous abortion, stillbirth, anticardiolipin antibody

Early fetal loss may be a result of a variety of causes including chromosomal abnormalities; however, the etiologic factors involved with many of these losses are unknown and are categorized as idiopathic.[1] Various investigators have shown an association between spontaneous abortion, intrauterine growth retardation, stillbirth, and the presence of antiphospholipid antibodies such as lupus-like anticoagulants and anticardiolipin antibody.[2-19] Some studies[2-5, 15, 16] have shown that elevated levels of anticardiolipin antibody (immunoglobulin G [IgG]) are associated with thrombosis and fetal loss. It is these factors, their mechanisms and processes, that have increasingly become a major focus of attention for the treatment of patients with unexplained reproductive failure or adverse pregnancy outcome.

The purpose of this article is to examine the strength of the association between poor pregnancy outcome and antiphospholipid antibodies, to review the current diagnostic methods, and to examine various therapeutic trials to provide recommendations for clinical care.

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Antiphospholipid antibody and pregnancy outcome

Lupus-like anticoagulant is an immunoglobulin of the IgG or immunoglobulin M (IgM) class with anticoagulant activity considered to result from its interference with the activation of the prothrombin activator complex (prothrombin, factors Xa and V, calcium), probably by inhibiting the interaction of the above-mentioned factors and phospholipids (Fig. 1).[18, 19] Patients with the lupus-like anticoagulant or anticardiolipin antibody usually do not have bleeding diatheses, but rather, exhibit a tendency toward thrombosis.[20-24]

Laurell and Nilsson[25] first suspected a relationship between lupus-like anticoagulant and biologic false-positive serologic test for syphilis and showed that the Kahn antigen (a venereal disease research laboratory–related antigen) was associated with lupus-like anticoagulant activity. However, it was Conley and Hartman[26] who first showed lupus-like anticoagulant in two patients with systemic lupus erythematosus associated with false-positive tests for syphilis. Whereas originally

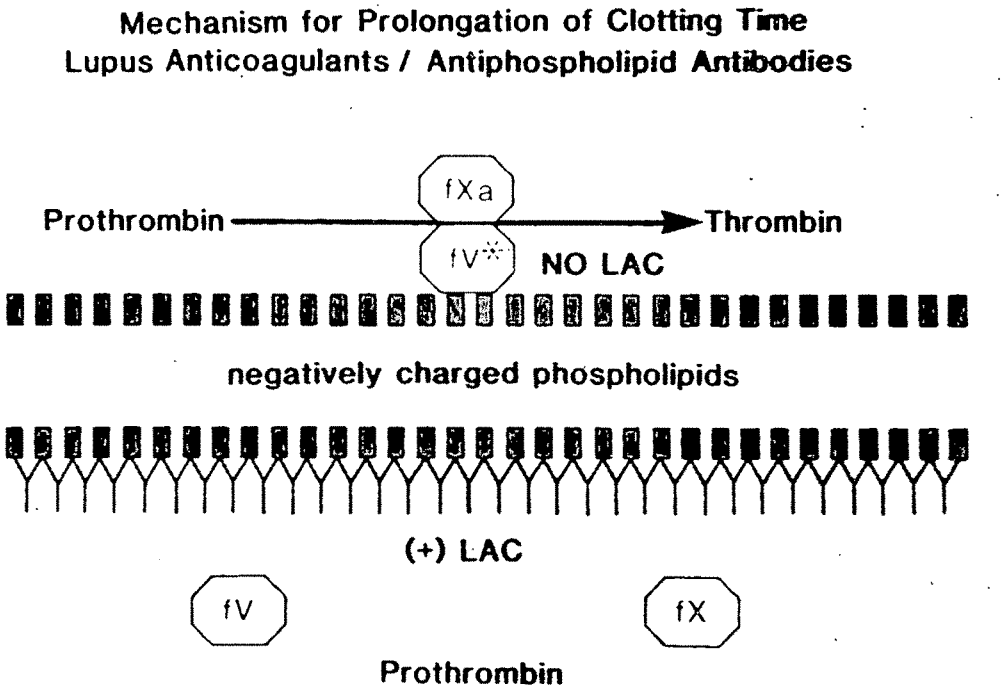


Fig. 1. Diagram of mechanism for lupus-like anticoagulant interfering with prothrombin complex.

detected in patients with systemic lupus erythematosus, the lupus-like anticoagulant has been subsequently found in association with other immunologic disorders and in patients with nonimmunologic diseases.[27]

Cardiolipin is the most active phospholipid in the venereal disease research laboratory assay systems. Antibodies responsible for lupus-like anticoagulant activity bind a variety of negatively charged phospholipids including cardiolipin,[18, 28-31] and this accounts for low-level false-positive venereal disease research laboratory test results in these patients. With the use of a solid-phase radioimmunoassay system to detect anticardiolipin antibody, Harris et al.[16, 30] showed these antibodies in a broad population of patients. More recently, reports have focused on the presence of antiphospholipid antibody, specifically the anticardiolipin antibody, in patients with subclinical autoimmune disease,[32] with systemic lupus erythematosus or with a history of recurrent abortion, thrombosis, or thrombocytopenia.[28, 32-39] Harris et al.[38] further emphasized that the anticardiolipin antibody (IgG subtype) level was predictive for fetal loss and thrombosis. The majority of patients with lupus-like anticoagulant, as identified by a functional coagulation assay, are also found to have anticardiolipin antibody, suggesting a strong link between the two groups of antibodies.[28] However, there are data to support that the anticardiolipin antibody is a better predictor of adverse pregnancy outcome than is the lupus-like anticoagulant.[40, 41] With the use of fetal death as the outcome variable, Lockshin et al.[40] reported a sensitivity for anticardiolipin of 0.85 and a specificity of 0.92.

It is estimated that about 20% to 30% of patients with systemic lupus erythematosus have an antibody to cardiolipin and are thereby at increased risk of vascular thrombosis in various organ systems. The biologic mechanism(s) by which thrombosis occurs is unknown. The inhibition of prostacyclin (PGI_2) production from endothelial tissues by fractions containing the antibody has been reported.[5, 21] This report was subsequently confirmed with aortic smooth muscle cell culture from rats.[21, 39, 42] The increased tendency toward thrombosis in patients with antiphospholipid antibodies may be a consequence of a number of factors including a decrease in fibrinolytic activity as a result of the inhibition of prekallikrein factor production,[43] acquired deficiency of proteins C and S, and antithrombin III activity.[44] Alternatively, inhibition of PGI_2 production by endothelial cells may be the common pathogenic mechanism leading to systemic thrombosis or the decidual vasculopathy observed in pathologic pregnancies.[21, 42] It also has been reported that the placentas of patients who experience adverse pregnancy outcome in the presence of antiphospholipid antibodies, particularly lupus-like anticoagulant, show extensive infarction.[42] Therefore, placental vasculopathy may be considered an expression of the generalized thrombotic process, resulting from an inhibition in the synthesis of prostacyclin, a natural antithrombotic agent.

Lockwood and colleagues[45] have examined the prev-

alence of lupus-like anticoagulant and anticardiolipin antibody in a low-risk population. This is of importance because the occurrence of normal outcomes in patients found to have high lupus-like anticoagulant or anticardiolipin antibody concentrations would discredit the role(s) of antiphospholipid antibodies in the pathogenesis of reproductive failure and adverse outcomes. In this study, which involved 737 sequential obstetric patients, Lockwood and colleagues[45] found that the presence of lupus-like anticoagulant in the general obstetric population was 2.7/1000, whereas the prevalence of anticardiolipin antibody was shown to be 22/1000. A number of patients were noted to have uncomplicated pregnancies despite the presence of antiphospholipid antibodies. However, increased levels of anticardiolipin antibody (IgG or IgM) resulted in higher incidences of adverse pregnancy outcomes.[45]

These data show that high titers of antiphospholipid antibodies do play a role in reproductive failure and adverse pregnancy outcome, although the precise mechanism remains undetermined. The occurrence of spontaneous abortions and the possible link to antiphospholipid antibodies may be underestimated because of the failure of patients to routinely seek prenatal care after an early pregnancy loss. The incidence of lupus-like anticoagulant as ascertained by a functional coagulation assay appears quite low in this population, but direct assay of the causative antibody (anticardiolipin antibody) reveals a prevalence of about 2% with affected patients. Such an association is significant inasmuch as a plausible explanation for certain adverse pregnancy outcomes was heretofore unknown.

Diagnosis

Clinical suspicion. The presence of antiphospholipid antibodies should be considered in cases of unexplained recurrent spontaneous abortions, intrauterine growth retardation, or stillbirth.[2-14] Indications for such investigation include a clinical suspicion of systemic lupus erythematosus, with or without associated venous or arterial thromboses by history; unexplained thrombocytopenia or hypoprothrombinemia; the presence of positive antinuclear antibodies, antismooth muscle antibodies or a false-positive venereal disease research laboratory test.[10, 46, 47] The confirmation of antiphospholipid antibodies can only be done through laboratory testing.

Laboratory diagnosis

Lupus-like anticoagulant. The lupus-like anticoagulant interacts with the phospholipid portion of the prothrombin activator complex. If plasma contains high levels of this immunoglobulin, the partial thromboplastin time (PTT) and occasionally the prothrombin time (PT) are prolonged. With the use of exponential dilutions of tissue thromboplastin, Boxer et al.[27] showed a more prolonged PT in patient plasma as opposed to control plasma at high dilutions of the tissue thromboplastin. However, there is evidence that the PTT is more sensitive than the PT, and in general, the PTT is the only abnormal hematologic parameter. This contrasts with the observed tendency toward thrombosis, which is thought to be mediated through platelet activation, an increase in thromboxane levels, and its impact on membrane phospholipid, causing a decrease in prostacyclin (Fig. 2). The test that is currently performed is the activated partial thromboplastin time (APTT) or the Russell viper venom time. Reece et al.[48] proposed a simple method for investigation of the cause of a prolonged APTT. If a patient has an unexplained prolonged APTT, normal plasma can be mixed with the patient's plasma, and if the APTT is corrected by this mixing of blood, a clotting factor deficiency should be suspected. If the APTT is not corrected, then the presence of circulating anticoagulants such as lupus-like anticoagulant should be considered. Lupus-like anticoagulant is confirmed if the APTT is corrected by addition of an increased amount of phospholipid[24] or by addition of freeze-dried platelets.[49] As mentioned previously, if no correction is observed, specific coagulation factor deficiency should be investigated (Fig. 3).

Anticardiolipin antibody. Anticardiolipin antibodies are demonstrated in patients' sera by solid-phase radioimmunoassay[28, 50] or, more recently, by enzyme-linked immunoassay tests.[46, 47] In brief, these methods involve coating wells of a plastic plate with cardiolipin then adding appropriately diluted patient's sera. If anticardiolipin antibody are present in the patient's sera, they will stick to the cardiolipin-coated wells, and their presence can be detected by the addition of radiolabeled antihuman antibodies or enzyme labeled antihuman antibodies. Since these tests were introduced, considerable improvements in their performance have occurred, and efforts are in progress for their standardization.[47, 51]

Other related tests. Antibodies to cardiolipin can give rise to biologic false-positive venereal disease research laboratory test results because the serologic tests also use phospholipid substrates. Antinuclear antibodies have been reported to occur in about 40% to 70% of patients with antiphospholipid antibodies. However, the original theory that nuclear and phospholipid epitopes are the same has been disproved.[16, 29, 30, 52] The presence of antidouble-stranded deoxyribonucleic acid (DNA) in the sera of patients with anticardiolipin antibody cannot be attributed to shared epitopes. Anti-DNA and antismooth muscle antibodies may also be present in patients with systemic lupus erythematosus. Similarly, lower titers of the C4 fraction of complement have also been reported in patients with systemic lupus

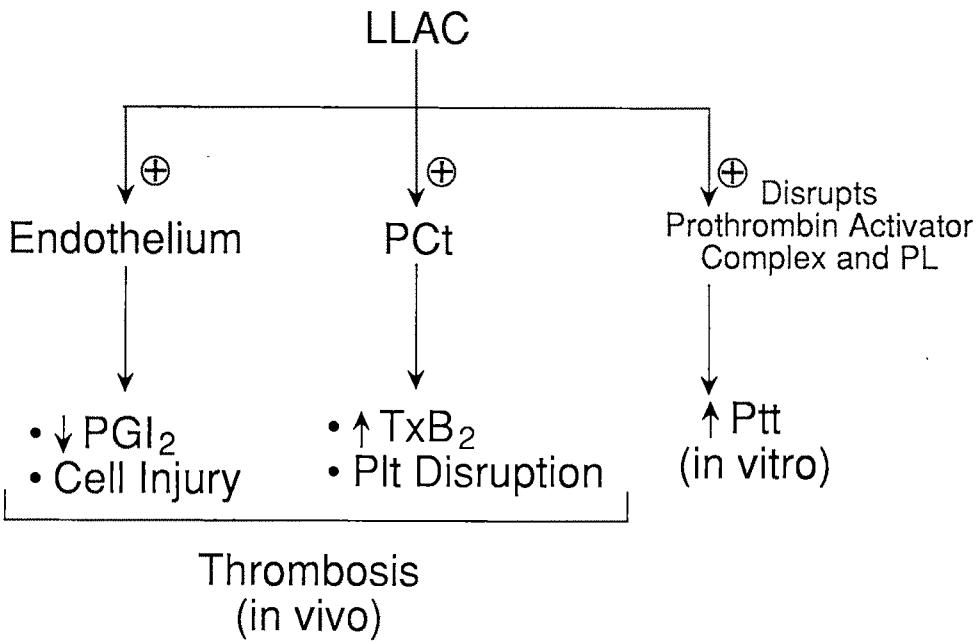


Fig. 2. Diagram of effect of lupus-like anticoagulant, which causes thrombosis in vivo and prolongation of partial thromboplastin time in vitro.

erythematosus and antiphospholipid antibodies.[53] In addition, there has been a suggestion that autoantibodies are associated with fetal loss, possibly through different mechanisms. For example, the anti-Ro may be through a congenital heart block mechanism and the anticardiolipin antibody may be through a placental ischemic mechanism.[54]

Treatment

There is no general agreement among investigators on the optimum treatment, if any, for high-risk patients with lupus-like anticoagulant or anticardiolipin antibody. In 1952 Conley and Hartman[26] used adrenocorticotropin hormone to obtain the disappearance of the lupus-like anticogulant. More recently, successful treatment protocols that use various combinations of high doses of corticosteroids and low-dose aspirin have been reported (Table I). The administration of corticosteroids suppressed the lupus-like anticoagulant as shown elsewhere.[26, 57, 65] Aspirin was added to counteract the increased tendency of platelets to aggregate and adhere, which may be responsible for the inclination toward thrombosis and adverse pregnancy outcomes.

In the literature to date there are several reports that chronicle the various therapeutic regimens (prednisone, aspirin, and heparin) and pregnancy outcome (Table I). The overall live birth rate with all forms of treatment was 66.9%. Further analysis revealed a live birth rate of 39% with steroid or azathioprine, 41.2% with steroid or azathioprine and heparin, and 79.1% with steroid or azathioprine plus aspirin.

Branch et al.,[8] with the use of a therapeutic protocol similar to that used by other investigators, found that a restoration to normal of the APTT did not ensure a live birth. Therefore, meticulous antepartum care was advised in view of the ever-present danger of preeclampsia, intrauterine growth retardation, and fetal death. With the use of high-dose corticosteroid and aspirin, Farquharson et al.[59] managed a patient who had a history of previous abortions and prolonged clotting time and in whom the mixing tests were consistent with the presence of lupus-like anticoagulant. The patient experienced a severe thrombosis of the right vertebral and posterior-inferior cerebellar arteries. The pregnancy was terminated. In light of this complication, the author suggested the initiation of therapy before conception. Controversy reigns, not only with regard to treatment regimens but as to whether or not to treat. Some investigators are reluctant to treat patients with high-dose corticosteroids and aspirin, citing the significant potential risk for maternal and fetal complications.[11, 12, 15]

In patients with both lupus-like anticoagulant and anticardiolipin antibody, a debate has ensued over which of the two groups of antibodies can be more easily suppressed with aspirin and corticosteroids and how this suppression, or the lack thereof, may relate to pregnancy outcome. Reports from various authors[15, 64, 66] showed that anticardiolipin antibody is more difficult to suppress but is a better prognostic indicator than lupus-like anticoagulant. However, Parke et al.[9] were able to achieve a good outcome after suppression

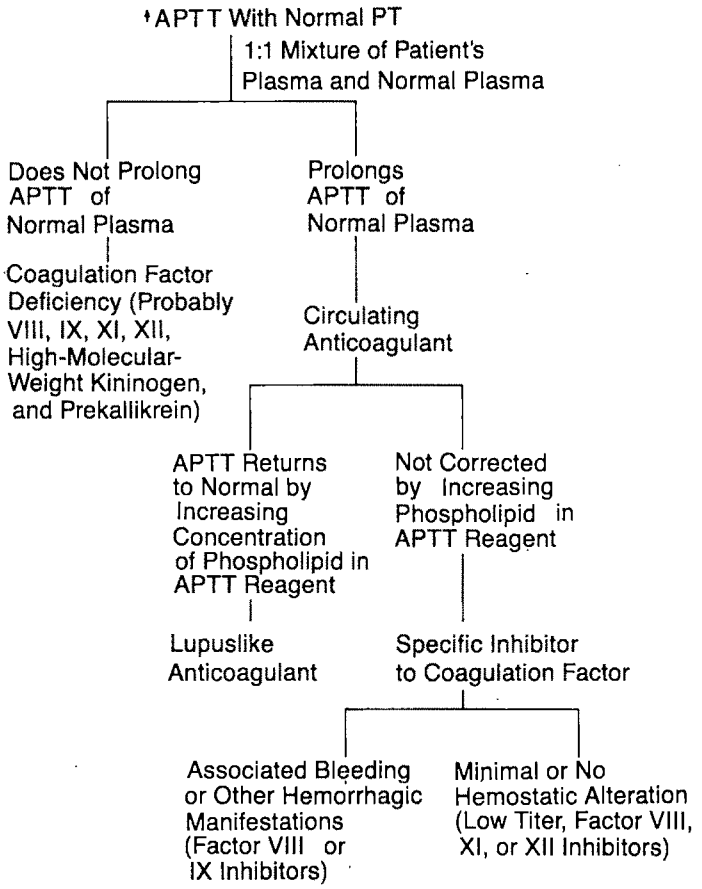


Fig. 3. Flow diagram depicts single method of evaluating patients with abnormal APTT, circulating anticoagulants, or factor deficiencies can be investigated by this means. (From Reece EA, Clyne LP, Romero R, Hobbins TC. Spontaneous factor XI inhibitors. Arch Intern Med 1984;144:525-9. Copyright 1984, American Medical Association. By permission.)

of anticardiolipin antibody in a patient with a history of five previous abortions. In this study high-dose corticosteroid was given before and throughout pregnancy. Serial measurements of anticardiolipin antibody and lupus-like anticoagulant antibodies were made and showed a continuous decline in anticardiolipin antibody concentrations, with the APTT eventually becoming normal. The dilute tissue thromboplastin inhibition test, chosen as a measure of the lupus-like anticoagulant, became prolonged when the patient became pregnant. At 27 weeks' gestation the patient had severe preeclampsia, necessitating premature delivery at 29 weeks' gestation. The neonate did not reveal anticardiolipin antibody in the peripheral blood, and the placenta was small with some infarcted areas.[9]

In another study by Norberg et al.,[59] the level of the APTT and/or anticardiolipin antibody concentration was shown not to be related to pregnancy outcome. The authors emphasized that high concentrations of anticardiolipin antibody may be transiently elevated also in patients with infectious diseases such as cytomegalovirus or human immunodeficiency virus infection. However, this association seems to be temporary and not significantly connected with any clinical or laboratory findings.

In our series (Unpublished data), live births occurred among 14 (77.8%) of our 18 patients with antiphospholipid antibodies and prior pregnancy losses treated with prednisone or low-dose aspirin during pregnancy. We also observed a unique association between the number of prior fetal losses, the anticardiolipin antibody titer, and the fetal survival rate after therapy. Two or more prior fetal losses and high autoantibody titer resulted in a fetal survival rate of 50% to 75% with varying therapeutic regimens and dosages. However, an improved fetal survival rate of 75% to 100% was observed with fewer than two prior fetal losses and low- to midanticardiolipin antibody titer with the same therapy.

As Table I shows, the treatment regimens used to date have employed various combinations of corticosteroid, heparin, and aspirin. In most cases, the outcome of the pregnancies improved with therapy. The optimum obstetric management and treatment remain unsettled. However, the latter is part of a large, ongoing multicenter clinical trial sponsored by the National In-

Table I. Treatment and pregnancy outcomes of pregnant patients with antiphospholipid antibodies and prior adverse outcomes

Investigators	*No. of patients*	*Treatment*	*Outcome*
Carreras et al. (1972)[21]	1	Prednisone 80 mg every day	PROM at 7 mo, stillbirth
Hartikainen-Sorri et al. (1980)[55]	1	Prednisone 5-10mg every day	Cesarean section at 37 wk, fetal distress, live birth
Hellgren et al. (1982)[56]	9	Heparin	5 SAB, 4 live births
Lubbe et al. (1983)[57]	1	Prednisone 60 mg/day and ASA 75 mg/day	Term live birth
Lubbe et al. (1983)[55]	6	Prednisone 40-60 mg/day; and ASA 75 mg/day	5 Live births; 1 fetal death at 16 wk
Ros (1983)[58]	2	Prednisone 30-60 mg every day	3 Live births
	2	Prednisone 30-60 mg every day and azathioprine 75 mg	1 fetal death
Farquharson et al. (1984)[59]	2	Prednisone 40-50 mg every day and ASA 75 mg every day	Both live births: (1) 34 wk PROM, SVD; (2) 30 wk fetal distress, cesarean section
Lockshin et al. (1984)[15]	28 (33 Pregnancies)	Prednisone and azathioprine	8 Elective abortions, 6 SVD at term, 11 preterm deliveries, 8 fetal losses
Lubbe et al. (1984)[7]	7	6 Prednisone 40-60 mg/day and ASA 75 mg/day; 1 heparin SQ and ASA 75 mg/day	6 Livebirths (4 SVD; 1 cesarean section) 1 SAB at 16 wk
Gardlund (1984)[60]	1	Heparin	Live birth
Junger et al. (1984)[61]	10	Corticosteroids	No outcome data
Branch et al. (1985)[8]	8	Prednisone 40-50 mg and ASA 81 mg every day	5 Live births (5 preeclampsia, 3 IUGR), 1 IUFD at 20 wks, 2 1st trimester AB
Lubbe et al. (1985)[2]	12	Prednisone 40-60 mg and ASA 75 mg	10 Live births; 2 SAB
Clauvel et al. (1986)[11]	3	Corticosteroids and 0.5 mg/kg/day	3 SAB
	1	Steroids 1 mg/kg/day and ASA 100 mg every day	1 Live birth (premature)
Parke et al. (1986)[9]	1	Prednisone 30 mg and heparin 500 mg twice daily and ASA 80 mg	Live birth at 29 wk, cesarean section and preeclampsia
Gregorini et al. (1986)[62]	1	Prednisone 30 mg and azathioprine 100 mg	Live birth at 34 wk, IUGR
Frampton et al. (1987)[63]	1	Prednisone 20-40 mg and ASA 300 mg 3/wk, plasma exchange 2/wk, dipyridamide 300 mg	Live birth at 34 wk
Hedfors et al. (1987)[64]	1	Prednisone 30-40 mg/day	First trimester SAB
Petrie et al. (1987)[12]	2	Prednisone 30 mg/day and ASA 75 mg/day	1 Live birth 1 IUFD at 25 wk
Norberg et al. (1987)[53]	5	Prednisone 30 mg and ASA 125-250 mg	5 Live births (1 IUGR)
Reece et al. (1989, Unpublished data)	18	Prednisone 20-60 mg/day and ASA 80 mg/day	14 Live births, 3 SAB, 1 stillbirth at 24 wk
Lockshin et al. (1989)[41]	21	Prednisone 30-60 mg/day and ASA 80 mg/day	4 Live births
Total number of pregnancies treated	Live births (%)	Elective abortion (%)	Total fetal losses (%)
139	83 (60.0)	8 (6.0)	48 (35.0)

ASA, Aspirin; *PROM*, premature rupture of the membranes; *SVD*, spontaneous vaginal delivery; *IUGR*, intrauterine growth retardation; *SQ*, subcutaneous; *SAB*, spontaneous abortion; *IUFD*, intrauterine fetal death.

*Excluded from calculations because no outcome data were available.

stitutes of Health in which we are engaged. In this study, low-risk patients (one or no losses and antiphospholipid antibodies) are randomized to usual care versus low-dose aspirin, and high-risk patients (two or more losses plus antiphospholipid antibodies) are randomized to aspirin plus heparin versus aspirin and prednisone.

Some investigators have suggested that antepartum fetal heart rate monitoring or Doppler ultrasonography may be useful in the identification of fetuses at risk of sudden death.[67, 68] The drawback in such reports includes the lack of a control population against which findings can be compared. However, from a practical standpoint, because these forms of tests are acceptable means of assessing fetal well-being, such are well advised for these at-risk patients.

Comment

In summary, reproductive failure and adverse pregnancy outcomes including recurrent abortions, intrauterine growth retardation and fetal death cannot always be explained. Recent evidence suggests that a small subset of patients with adverse pregnancy outcomes, previously categorized as idiopathic, may have high concentrations of antiphospholipid antibodies.

Cardiolipin is the primary epitope of the antiphospholipid antibody family, being present in many cases of unexplained recurrent adverse pregnancy outcomes. Assays for anticardiolipin antibody activity appear to be the optimal screening tool for identification of patients at risk of the aforementioned pregnancy outcomes. Therapeutic protocols based on aspirin, corticosteroids, or heparin have been successfully used.[69] However, because maternal and fetal complications have been reported in patients who receive such therapy, extreme caution must be exercised. The ad hoc use of treatment protocols, without appropriate consultation, should be discouraged until further studies are conducted to elucidate the optimum therapeutic regimens, dosages, timing, and duration of therapy.

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The effect of adrenocorticotropic hormone infusion on subsequent pituitary response in the sheep fetus

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It is not known whether activation of the fetal adrenal gland can inhibit pituitary adrenal responses to stress. Therefore we treated 14 chronically cannulated sheep fetuses (gestational age range, 109 to 129 days) with an adrenocorticotropic hormone infusion of 5 ng/kg per minute or vehicle solution at similar rates for 2.5 hours and then subjected them to a 10-minute period of hypotension. Resting mean arterial blood pressures were similar for both control and adrenocorticotropic hormone infusion groups and decreased similarly after administration of sodium nitroprusside. Resting fetal plasma cortisol levels (11.6 ± 3.3 ng/ml) and adrenocorticotropic hormone (42 ± 15 pg/ml) concentrations were not different in the two groups. In the control group fetal plasma cortisol concentrations rose from 12.1 ± 1.7 to 35.7 ± 8.0 ng/ml after hypotension ($p < 0.05$) and plasma adrenocorticotropic hormone increased from 37 ± 19 to 145 ± 67 pg/ml ($p < 0.05$). In the group treated with adrenocorticotropic hormone, fetal plasma cortisol concentrations increased (30.2 ± 7.8 to 53.6 ± 15.0 ng/ml; $p < 0.05$) after hypotension whereas fetal plasma adrenocorticotropic hormone concentrations did not increase (398 ± 227 versus 258 ± 77 pg/ml; $p > 0.05$). (Am J Obstet Gynecol 1990;163:170-4.)

Key words: Pituitary-adrenal axis, adrenocorticotropic hormone, stress

The ontogeny of pituitary development in the sheep fetus has been examined by studying the response of the fetus to hypoxemia and hypotensive stress induced by hemorrhage, and more recently to hypotension induced by sodium nitroprusside (Nipride).[1, 2] Studies have shown that there is earlier development of the adrenocorticotropic hormone (ACTH) response to stress with accompanying cortisol response occurring later in gestation.[3] The existence of a feedback relationship has been studied by the administration of exogenous cortisol and examination of its effect on the subsequent pituitary-adrenal response to stress.[4] This relationship has also been examined by stimulation of the pituitary gland with corticotropin-releasing factor after cortisol infusion at varying gestational ages.[5] Until this time the exogenously administered cortisol has been assumed to be of a physiologic amount on the basis of basal cortisol levels. Because cortisol production by the fetus is thought to be minimal until after 121 days[6] and yet there is ACTH responsiveness much earlier[7] this study was conducted to assess whether the sheep fetus at 109 to 129 days' gestation can increase endogenous cortisol levels sufficiently to exert negative feedback effects on stress-stimulated ACTH production.

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Material and methods

A total of 24 fetal lambs were surgically instrumented at a gestational age between 109 and 128 days. Polyvinyl catheters were placed in the fetal and maternal inferior vena cava and distal abdominal aorta via femoral vessels.

Fetal status was monitored with arterial blood gas evaluation intraoperatively and on a periodic basis postoperatively. The animals were allowed to stabilize 3 to 5 days before study. The experimental protocol consisted of a 2.5 hour ACTH infusion at 5 ng/kg per minute for a total volume of 20 ml or a control infusion of 0.1% bovine serum albumin in saline solution. Before the infusion the ewes and fetuses were allowed to stabilize for 40 minutes after being connected to the hemodynamic monitoring equipment. Fetal arterial blood pressure, heart rate, and amniotic fluid pressure

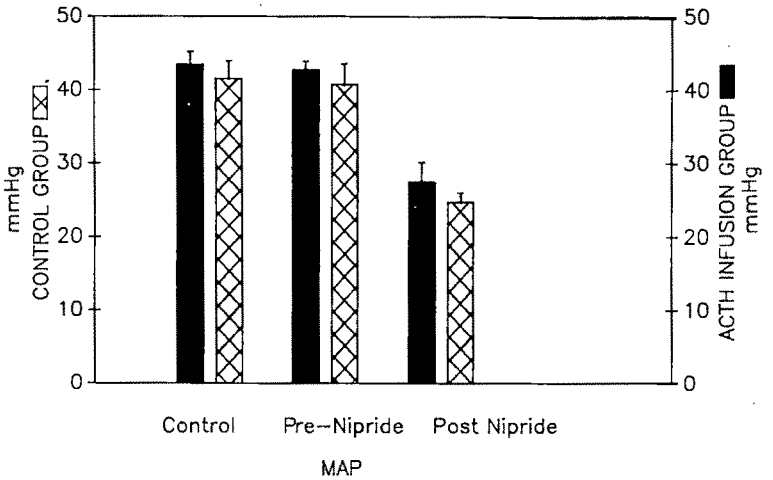


Fig. 1. Fetal mean arterial blood pressure during experiment.

were monitored continuously during the experiments. Samples were taken at periodic intervals from the fetus for cortisol, ACTH, arterial blood gas, and hematocrit evaluations. The sample volume was 2.5 ml whole blood and the sample volume was replaced with an equivalent volume of saline solution to maintain euvolemia. Cortisol and ACTH samples were collected in tubes that contained ethylenediaminetetraacetic acid and were immediately placed on ice. The samples were then centrifuged. The plasma was collected and frozen at −20° C until assay. At the completion of the ACTH or control infusion, an infusion of control solution was started or continued for an additional 30 minutes before hypotension was induced by sodium nitroprusside. Then an infusion of sodium nitroprusside was begun at a rate sufficient to lower the fetal mean arterial blood pressure by approximately 40%. This infusion was continued for a total of 10 minutes at which time the final samples for ACTH, cortisol, hematocrit, and arterial blood gas evaluation were taken and the infusion was stopped.

Plasma cortisol concentrations were measured with a previously described radioimmunoassay.[2] Plasma ACTH levels were analyzed in unextracted plasma by radioimmunoassay with commercially available reagents (Immunonuclear).

Blood pH, P_{O_2}, and P_{CO_2} were measured with a blood gas analyzer (model ABL 30, Radiometer, Copenhagen, Denmark.)

All fetal blood pressures were calculated with amniotic fluid pressure as a zero reference. Pressures and heart rate were sampled by microcomputer and an appropriate analog to digital converter and were averaged for 60-second intervals except during the sodium nitroprusside infusion when samples were averaged at 30-second intervals. A continuous strip chart recording of the same parameters was also maintained during the experiment. Fetal plasma cortisol and ACTH levels were compared immediately before and after the sodium nitroprusside infusion. Because of sample inhomogeneity of variance, the Wilcoxon paired sample test was used to statistically analyze the results. Similar time interval comparisons were made of blood pressure, pH, P_{O_2}, P_{CO_2}, and maternal cortisol values. Statistical analyses of these parameters were by analysis of variance.

Results

Initially 24 animals were studied with 12 in each group, ACTH or control. After examination of fetal blood gas data, five animals were eliminated from each group because of blood gas values that indicated acidosis, hypoxemia, or hypercapnia (pH <7.2, P_{O_2} <15 mm Hg, P_{CO_2} >55 mm Hg).

Analysis of the hemodynamic variables of the remaining animals did not reveal statistically significant differences in fetal mean arterial blood pressures or heart rate over the course of the ACTH or control saline solution infusions. During the infusions of sodium nitroprusside there were similar reductions in mean arterial blood pressure. In the ACTH group blood pressure declined 15 ± 2 mm Hg (36%) and in the control group 16 ± 2 mm Hg (38%). These were not statistically different (Fig. 1).

Blood gas values from the fetuses after elimination of the abnormal animals were not different between groups (Table I).

Statistical analysis of the cortisol concentrations from each group showed a significant rise over the course of hypotension induced by sodium nitroprusside. The fetal plasma cortisol levels in the ACTH group rose from 30.2 to 53.5 ng/ml ($p < 0.05$) and in the control group the fetal plasma cortisol levels rose from 21.1 to 35.6 ng/ml ($p < 0.05$). The ACTH group showed a rise in fetal plasma cortisol levels over the course of the

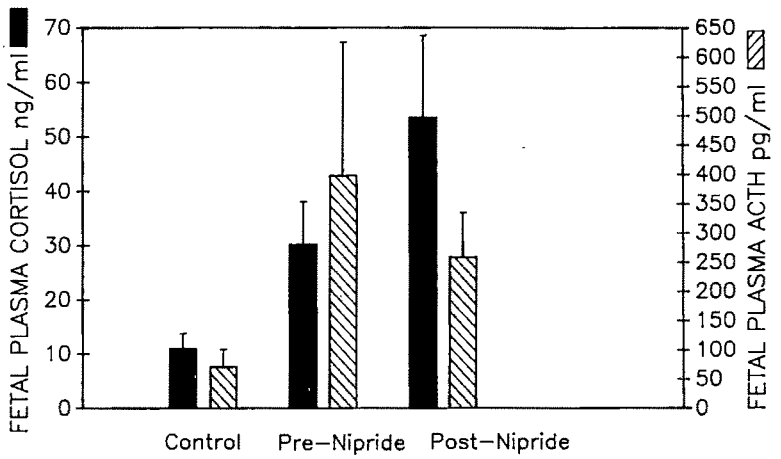


Fig. 2. Fetal plasma cortisol and ACTH levels during experiment in ACTH infusion group ($n = 7$).

Table I. Fetal blood gas data during experiment

	Control group ($n = 7$)			*ACTH infusion group ($n = 7$)*		
	Control	*Before sodium nitroprusside*	*After sodium nitroprusside*	*Control*	*Before sodium nitroprusside*	*After sodium nitroprusside*
pH	7.34 ± 0.01	7.33 ± 0.02	7.32 ± 0.04	7.34 ± 0.01	7.32 ± 0.01	7.31 ± 0.01
P_{O_2} mm Hg	20.8 ± 0.8	21.2 ± 0.8	23.1 ± 1.4	18.9 ± 1.0	17.9 ± 1.1	20.6 ± 0.9
P_{CO_2} mm Hg	44.4 ± 1.5	43.1 ± 2.7	45.1 ± 3.7	48.0 ± 1.2	47.8 ± 2.0	49.4 ± 2.1

ACTH infusion. No consistent change was found in fetal plasma cortisol concentration during the saline solution–bovine serum albumin infusion in the control group. The fetal plasma ACTH concentration in the control group showed no change until after hypotension was induced by sodium nitroprusside and then rose from 37 ± 19 to 145 ± 67 pg/ml ($p < 0.05$). In contrast, plasma ACTH concentration in the ACTH infusion group showed no significant change after hypotension was induced by sodium nitroprusside (Figs. 2 and 3).

Comment

Multiple investigators have examined the developmental aspects of the pituitary-adrenal axis. Sheep fetuses at varying gestational ages were subjected to hypotensive stress and the effect on ACTH and vasopressin were examined. These studies showed an ACTH response as early as 95 days' gestation but attenuated cortisol response until 109 days' gestation.[2] In the group >123 days' gestation basal ACTH concentrations were lower but cortisol levels were higher. Other studies have shown that ACTH production in response to corticotropin-releasing factor exists as early as 95 days' gestation but cortisol production remains modest until 125 days' gestation.[5,7] In these studies basal cortisol levels were higher at 135 days' gestation with decreased ACTH responses to stimulation by corticotropin-releasing factor. Before that gestational age it is uncertain whether the fetus can respond to ACTH stimulation with sufficient cortisol production to cause feedback on ACTH production.

Specific effects of increased cortisol levels on fetal stress responses have been shown by the administration of cortisol to sheep fetuses in physiologic amounts. Studies have shown that cortisol infusions to sheep fetuses between 94 and 131 days' gestation diminished ACTH responses to hypotensive stress.[4,8] Glucocorticoid suppression of the fetal ACTH response to corticotropin-releasing factor or arginine vasopressin administration has also been shown in the sheep fetus by 113 days' gestation.[9-11]

Results in this study are consistent with those cited in that ACTH-induced cortisol secretion is shown over a gestational range of 109 to 129 days. ACTH responsiveness to hypotensive stress is similarly shown. Furthermore, this study illustrates that ACTH administration can increase fetal plasma cortisol levels sufficiently to attenuate an ACTH response to stress. An argument could be made that the ACTH levels achieved during stress induced by sodium nitroprusside represents a maximal output of ACTH by an immature pituitary as opposed to decreased ACTH production as a result of cortisol feedback on the pituitary gland. Recent studies investigating the decreasing sensitivity of the pituitary gland to negative feedback in gestations close to term

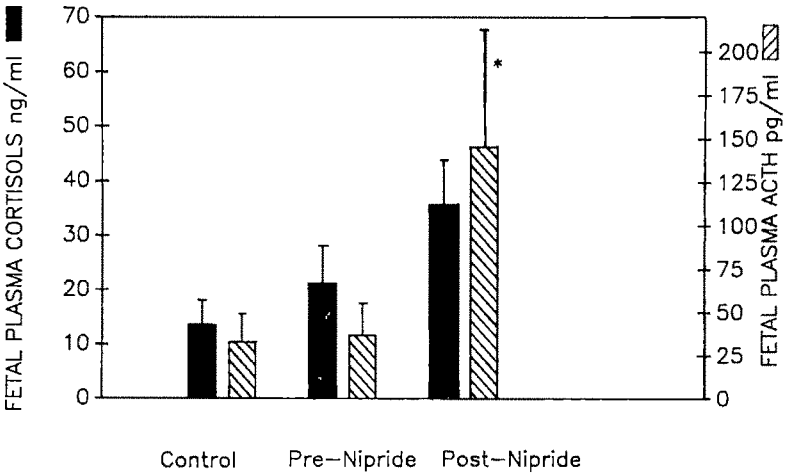


Fig. 3. Fetal plasma cortisol and ACTH levels during experiment in control group ($n = 7$). *Asterisk* indicates statistical significance.

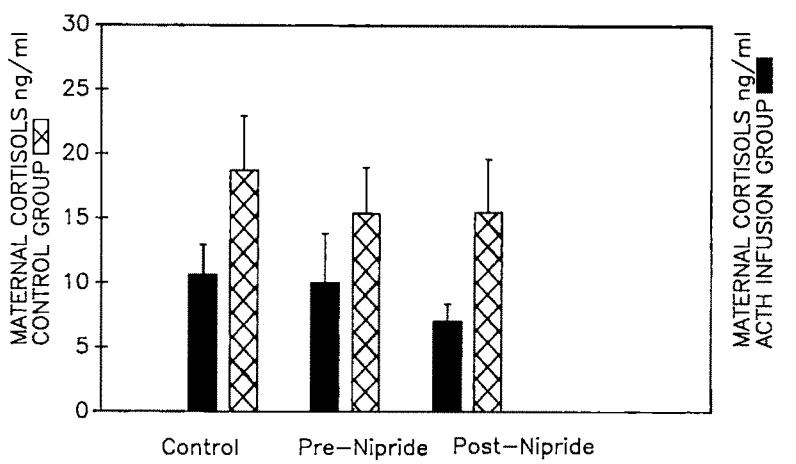


Fig. 4. Maternal plasma cortisol levels during experiment.

have shown that ACTH production in sheep can surpass 1000 pg/ml in response to hypotension induced by sodium nitroprusside.[12] Therefore it is believed that the ACTH levels in response to stress in this study represent submaximal production as a result of feedback inhibition. Other studies have similarly shown high ACTH levels in response to hypoxemia.[1]

Unexpectedly, the fetal cortisol response to stress was not attenuated by ACTH pretreatment. Several studies have shown that with pituitary-adrenal maturation occurring after 110 days of gestation there are two changes that affect ACTH and cortisol production. Stimulation of corticotropin-releasing factor produces less of an ACTH response as the fetus approaches term. However, adrenal responsiveness to ACTH increases such that there is a higher basal level of cortisol, resulting in increased negative feedback on ACTH production.[3, 7] In vivo and in vitro studies have shown that prolonged stimulation of the fetal adrenal by ACTH administration results in priming of the fetal adrenal and that further stimulation of the adrenal either in vivo or in vitro with dispersed pretreated adrenal cells produces greater cortisol production.[5, 13-15] Such a priming effect may have influenced cortisol levels in these experiments.

Because of the known contribution of maternal cortisol to the fetal cortisol level in early gestation the cortisol levels in the ewe were monitored during the course of the experiment. It is known that until 121 days' gestation maternal cortisol contributes a large proportion to the fetal cortisol level by placental transfer.[6] Thus high maternal levels could alter the fetal levels and exert negative feedback on the fetal adrenal gland. In this study the maternal cortisol levels did not show a trend in either group during the course of the experiment although they were higher in the control

study animals. Even with somewhat higher maternal cortisol levels the group of control animals showed the expected ACTH response to stress and therefore the maternal levels had no detectable effect on the control group (Fig. 4).

Another explanation for the presence of an increase in cortisol levels without an increase in ACTH can be found in the fact that some studies have shown that peptides other than ACTH may stimulate the fetal adrenal gland. Studies have shown that a rise in cortisol concentration occurs after the administration of melanocyte-stimulating hormone to newborn lambs.[16] Recent studies have also shown immunoreactive ACTH does not necessarily include the total amount of bioactive ACTH, although the difference is more pronounced in early gestation than at term.[17]

Finally, the time course of any ACTH response, and to a lesser extent cortisol response, may have been altered by the ACTH infusion so that sample timing after the infusion of sodium nitroprusside may not coincide with an increase in the plasma ACTH level. If that were the case, sampling at the end of the sodium nitroprusside infusion could possibly miss detection of an acute ACTH response that occurred at the onset of the hypotension induced by sodium nitroprusside. This seems unlikely because studies in adult dogs in which the pituitary-adrenal axis was stimulated with ACTH and then stressed with hypoglycemia showed that the subsequent ACTH response was both blunted and delayed such that the sampling at 10 minutes of stress detected the ACTH response.[18]

In summary, this study shows that at 109 to 129 days' gestation in the sheep fetus cortisol levels are modest and can be increased by ACTH. This increase in cortisol concentration is sufficient to modify the pituitary response to hypotensive stress by a negative feedback relationship. This study is in agreement with previous studies that show decreased ACTH production in response to stress or corticotropin-releasing factor when circulating fetal cortisol levels are increased by cortisol infusion.

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Changes in platelet angiotensin II binding sites associated with the human menstrual cycle

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We have shown a significant decrease in platelet angiotensin II binding site concentration associated with the luteal phase of the menstrual cycle ($p < 0.02$). (AM J OBSTET GYNECOL 1990;163:175-6.)

Key words: Angiotensin II, platelet membrane glycoproteins, renin-angiotensin system

Human platelet angiotensin II receptors have been found to respond to sodium intake–induced changes in plasma angiotensin II concentration in a similar manner to that of receptors in arterial muscle.[1] Increased platelet angiotensin II binding in human pregnancy has been reported,[2] and we have noted that these pregnancy-induced changes commence in the first few weeks of pregnancy (Unpublished observations). The purpose of this study was to determine whether the menstrual cycle was associated with alterations in platelet angiotensin II binding site levels.

On two occasions 40 ml of venous blood was taken from 15 women (aged 20 to 42 years; median, 25 years). The first sample was taken between days 5 to 9 of the menstrual cycle and the second sample was obtained on day 21. All the subjects were normotensive, gave a history of regular cycles, and were not taking medication or oral contraceptives. Approximately 20 ml of blood was used to determine platelet angiotensin II binding, as previously described.[1] Serum urea and electrolytes, angiotensin II, renin substrate, renin concentration, and progesterone estimations were performed with the remaining blood.

A rise in serum progesterone level from <5 nmol/L at days 5 to 9 to >30 nmol/L at day 21 was adjudged to indicate ovulation.

Fig. 1 summarizes the changes in platelet angiotensin II binding sites. In the ovulatory patients there was a significant fall in binding site concentration ($p < 0.02$, Wilcoxon nonparametric paired test) from a median value of 11.2 fmol/10^9 cells at days 5 to 9 to a median value of 3.6 fmol/10^9 cells at day 21. There was also a significant rise in both the median values of plasma angiotensin II (from 9.4 to 16.5 pg/ml, $p < 0.05$), and in median values of plasma renin concentration (from 1.6 to 4.9 μmol, $p < 0.05$). The rise in plasma renin substrate was not statistically significant.

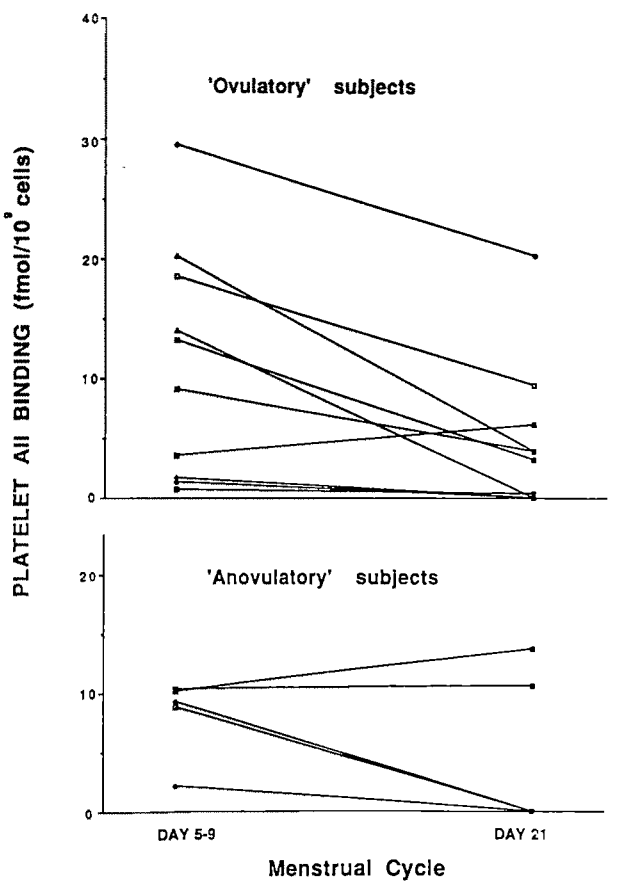


Fig. 1. Platelet angiotensin II binding site concentration in human menstrual cycle.

An increase in binding site concentrations was found

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in two of the five patients deemed to be anovulatory. Despite the small numbers, a significant difference in the change in plasma angiotensin II was shown in these patients as compared with the ovulatory patients, with the median value of plasma angiotensin II falling from 29.0 to 15.6 pg/ml ($p < 0.05$, Mann-Whitney U test).

Thus this study suggests that the elevated levels of the components of the renin-angiotensin system in the normal menstrual cycle are accompanied by reduced levels of angiotensin II binding sites on platelets (a suggested model of vascular smooth muscle[1,2]).

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Preventing cervical conization by achieving satisfactory colposcopy with hygroscopic cervical dilators

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Eighteen women with abnormal cervical cytologic findings and unsatisfactory colposcopic examinations underwent cervical dilatation with Dilapan (Gynotech), a hygroscopic dilator. Dilatation exposed the entire squamocolumnar junction, converting an unsatisfactory colposcopic examination into a satisfactory one and avoiding cervical conization in 17 of the patients. (Am J Obstet Gynecol 1990;163:176-7.)

Key words: Dilapan, unsatisfactory colposcopy, cone biopsy

Since the advent of colposcopy, the frequency of cone biopsy for the evaluation of cervical cancer and intraepithelial neoplasia has decreased significantly. Nonetheless, a significant number of cone biopsies are performed each year in the United States because of unsatisfactory colposcopy. Colposcopy is considered unsatisfactory if the entire transformation zone or each of the areas of atypical cervical epithelium cannot be completely visualized. Unsatisfactory colposcopy occurs in an estimated 10% to 15% of all women less than 45 years of age with abnormal cervical cytology and occurs even more frequently in postmenopausal women.[1] In these individuals a cervical conization is performed for histologic diagnosis; as a result, one in six women with cervical dysplasia will require a cone biopsy. A cone biopsy may result in an incompetent cervix in pregnancy and an increased risk of premature labor. Subsequent cervical evaluations may be hampered secondary to ascension of the squamocolumnar junction into the endocervical canal. Other problems include bleeding, infection, anesthesia risks, and cost.

We report the results of a simple technique: dilatating the cervix with Dilapan (Gynotech, Salem Industrial Park, Lebanon, N.J.), a hygroscopic cervical dilator, to convert unsatisfactory colposcopy into a satisfactory colposcopic examination.

Material and methods

Eighteen consecutive premenopausal women undergoing colposcopic evaluation under the supervision of the senior author for an abnormal Papanicolau smear had unsatisfactory colposcopic examinations even after using an endocervical speculum. The patients were premedicated with oral prostaglandin synthetase inhibitors and the cervix was prepped. One Dilapan cervical dilator was inserted just past the external os without penetrating the internal os. The dilator was left in place for 1 to 2 hours. Patients either waited in the waiting room or left the office to return at a designated time. After removal of the dilator with a ring forceps, colposcopic evaluation was repeated.

Results

The entire transformation zone was visualized in 17 of 18 patients undergoing cervical dilation. Cramping

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was minimal and no significant complications, including infection, occurred. Early in the study, one Dilapan cervical dilator broke off in the cervical canal during removal. The fragments were easily removed with a packing forceps.

Comment

Dilapan is a hema polymer dilator with hydrophilic properties similar to traditional laminaria japonica; however, it expands more rapidly. It may be used in clinical settings suitable for traditional laminaria and may be preferred due to its rapid action.[2] The Dilapan we used measured 3 mm in diameter and 25 mm in length. When exposed to physiologic saline solution or cervical mucus, its diameter quickly increases from 3 to 8 to 10 mm. Previous use of Dilapan has not resulted in significant morbidity, and its efficacy at cervical dilatation has been documented in early pregnancy terminations.[2] Insertion of one Dilapan cervical dilator at a cost of $6 resulted in enough dilation to convert a colposcopic examination that was unsatisfactory even with an endocervical speculum into a satisfactory examination. The patients were comfortable and the examination could be completed in a short time. Within 2 hours a definitive diagnosis and recommendations for further therapy can be made; standard laminaria, on the other hand, take approximately 6 hours to fully expand.

We recommend this simple procedure in the evaluation of women with abnormal cytology and unsatisfactory colposcopy despite using an endocervical speculum.

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Sharing of human leukocyte antigens in primary and secondary recurrent spontaneous abortions

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The prevalence of recurrent fetal loss and its relationship to sharing of human leukocyte antigens within couples was examined in a large, ethnically homogeneous Chinese population in Taiwan: 91 couples with primary recurrent spontaneous abortion, 32 couples with secondary recurrent spontaneous abortion, and 51 normal fertile couples. There was an excess of human leukocyte antigen sharing in both types of recurrent aborters. The primary aborters shared human leukocyte A and DQ antigens and three or more of the human leukocyte A, B, DR, and DQ antigens. The secondary aborters did not have an excess of sharing at any one locus but they did share three or more of the human leukocyte A, B, DR, and DQ antigens. There was no excess of antipaternal cytotoxic antibodies in any group of aborters, and the primary aborters had a lower level of mixed lymphocyte reaction blocking factor than normal couples or secondary aborters. Previous studies showed that couples in whom a gestational trophoblastic tumor developed in the woman shared human leukocyte B and DQ antigens and three or more of the human leukocyte A, B, DR, and DQ antigens. These studies provide substantial support for the role of recessive genes linked to the major histocompatibility complex in the pathogenesis of recurrent spontaneous abortions and of gestational trophoblastic tumors. (Am J Obstet Gynecol 1990;163:178-88.)

Key words: Human leukocyte antigen sharing, primary recurrent spontaneous abortion, secondary recurrent spontaneous abortion, genetics of reproduction, genetics of cancer

There is a considerable amount of literature with regard to both human beings and experimental animals on the cause of recurrent spontaneous abortion in the absence of anatomic, chromosomal, or hormonal abnormalities and infections. A variety of studies, but not all of them, indicate that there is a higher prevalence of sharing human leukocyte antigens (HLA) between husband and wife in these couples than there is in normal fertile couples.[1, 2] However, the difficulties with many of these studies are the relatively small number of couples examined and the unspecified or mixed ethnic composition of the populations. These variables could confound the statistical and genetic interpretation of the data. Nonetheless, the analysis of the aggregated data strongly supports the conclusion that there is a greater HLA sharing in couples in whom the woman experiences recurrent pregnancy losses. There are also reports that women who have had recurrent spontaneous abortions with one partner may not have them with another partner.[3] These observations are consistent with our hypothesis about the relationship between recurrent fetal losses and susceptibility to cancer and recessive genes linked to the major histocompatibility complex.[1, 4-7]

To test this hypothesis directly, we undertook a series of studies in a large, ethnically homogeneous Chinese population in Taiwan. The first study[8] showed that there was a significant level of HLA sharing in couples in whom a gestational trophoblastic tumor developed in the woman: the sharing involved HLA-B, HLA-DQ, and three or more of the HLA-A, B, DR, and DQ antigens. The present study examines HLA sharing in the couples from this same population who underwent primary or secondary recurrent spontaneous abortions, and it shows that there is a significantly increased level of HLA sharing in these couples when compared with normal fertile couples in the same population. Thus,

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6/1/20003

Table I. HLA typing of the couples with primary recurrent spontaneous abortions

Patient			*HLA specificity*				*Number of loci with shared HLA antigens**	
No.	*No. of abortions*	*Sex*	*A*	*B*	*DR*	*DQ*	*ABDR*	*ABDRDQ*
PA1	3	F	2,11	75,60,w6	12,4,w52	w7	3	4
		M	2,11	75,27,w6,w4	12,5,w52	w7,w3		
PA2	4	F	2	60,44,w4,w6	5,w52	w7,w2,w3	1	2
		M	24,11	27	5,12,w52	w7,w3		
PA3	4	F	24,2	35,w6	4,9,w52,w53	w3,w7	2	3
		M	24,11	13,60,w4,w6	4,12,w52,w53	w3		
PA4	3	F	2,24	70,48,w6	2,14,w52	w1	2	3
		M	2	60,w6	2,9,w53	w1		
PA5	4	F	11,24	13,60,w6	2,5,w52	w3,w1	1	1
		M	11	62,46,w6	4,9,w53	†		
PA6	4	F	24,11	54,60,w6	4,w53	w3,w4	2	3
		M	24,11	63,46,w6	4,12,w52,w53	w3		
PA7	3	F	11,2	39,50,w6	2,7,w53	w1,w2	2	3
		M	11,24	13,60,w4,w6	2,4,w52	w1		
PA8	5	F	11,31	58,60,w4,w6	3,4,w52	w3,w2	1	2
		M	11,2	51,46,w4	12,w52	w3		
PA9	3	F	24,11	55,60,w6	4,w53	w3	1	2
		M	24,2	62,46,w6	2,9,w53	w3,w1		
PA10	5	F	11,24	13,62,w4,w6	2	w1	1	2
		M	11,33	58,52,w4,w6	14,w52	w1		
PA11	4	F	11,31	60,w6	4,12,w52,w53	w3,w1	2	3
		M	11,2	60,50,w4	8,w52,w53	w3		
PA12	4	F	11,33	58,w4	3,w52	w3,w2	1	2
		M	11	60,27,w4,w6	4,14,w52,w53	w3,w1		
PA13	5	F	2,33	39,58,w4	3,4,w52,w53	w3	2	2
		M	2	46,56,w4	3,w52	†		
PA14	4	F	2,33	62,35,w6	4,9,1,w53	w3,w1	1	2
		M	24,11	60,w6	4,9,w53	w3		
PA15	4	F	11	60,13,w4,w6	4,5,w52,w53	w3	2	2
		M	11,24	60,62,w6	2	w1		
PA16	8‡	F	1,2	50,52,w4,w6	7,2,w53	w1	1	1
		M	24,30	13,58,w4	7,3,w52,w53	w2		
PA17	3§	F	11,2	60,38,w4,w6	2,4,w53	w1,w3	3	4
		M	11,24	60,55,w6	2,9,w53	w1,w3		
PA18	3	F	2,11	13,w4	2,w52	w1,w3	0	1
		M	32,33	44,51,w4	1,14,w52	w1		
PA19	5	F	2,11	46,60,w6	4,14,w52,w53	w1	2	2
		M	2,23	46,w6	5,w52	w3,w7		
PA20	4	F	24	55,67,w6	9,w53	w1,w3	0	1
		M	26,31	38,62,w4	1,2	w1		
PA21	5	F	2,33	51,57,w4	9,3,w52,w53	w3,w1	2	3
		M	11	51,57,w4	9,w52,w53	w3		
PA22	3‖	F	11	7,46,w6	7,12,14,w52	w7,w2	2	3
		M	11	55,60	7,5,w52	w7		
PA23	3	F	2,24	44,58,w4	3,10,w52	w1,w2	0	1
		M	11	60,w6	2,5,w52	w1,w3		
PA24	4	F	11,24	60,w6	4,14,8,w52,w53	w1	2	2
		M	11	62,46,w6	4,9,w53	w3		
PA25	3	F	11	62,67,w6	9,12,w52,w53	w3,w2	1	2
		M	11,2	51,w4	5,w52	w3		
PA26	4	F	11,24	44,75,w4,w6	12,w53	w3,w7	0	1
		M	33,31	53,58,w4	1,5,w52	w3,w7,w1		
PA27	8	F	2	13,46	2,3,w52	w1,w3	1	2
		M	2,11	38,52	4,14	w1		
PA28	3	F	11,33	58,60,w4	4,7,w52	w3,w2	0	1
		M	1,2	13,w4	12,w52,w53	w3,w1		

*Exclusive of Bw4,Bw6 and DRw52,DRw53.

†Blank; therefore, it is different from the other DQ antigen typed.

‡Intrauterine fetal death twice.

§Intrauterine fetal death once.

‖Mole once.

Table I—Cont'd

Patient			*HLA specificity*				*Number of loci with shared HLA antigens**	
No.	*No. of abortions*	*Sex*	*A*	*B*	*DR*	*DQ*	*ABDR*	*ABDRDQ*
PA29	3	F	11,24	63,60,w6	2,4,w53	w1	3	3
		M	11	63,38,w4,w6	2,9,12,w52,w53	†		
PA30	4	F	11,33	46,51,w4	9,w52,w53	w1,w3	2	3
		M	2,24	46,56	9,4,w53	w1,w3		
PA31	3	F	24,2	38,46,w4	2	w3,w1	1	2
		M	24,33	58,60,w4	3,9,w52,w53	w3		
PA32	3	F	11,24	57,62,46,60	2,9,w53	w1,w3	2	3
		M	11,2	39,54,w4	2,6,w52	w1,w3		
PA33	3‖	F	2	7,58,w4	3,7,w52,w53	w2	2	2
		M	2	46	3,5,w52	†		
PA34	3	F	11,31	57,51,w4	3,5,w52	w3,w2	1	2
		M	2	57,62,46	8,12,w52	w3,w1		
PA35	5	F	2	60	12,4,w52,w53	w3	1	2
		M	24,11	56	12,2,w52	w3,w1		
PA36	3	F	11,1	57,55,w4	7,14,w52	w1	1	1
		M	11,2	58,46,w4	3,9,w52,w53	w2		
PA37	4	F	2,33	58,60,w4,w6	12,2,w52	w1,w3,w7	1	2
		M	26,11	13,46	12,9,w53	w1,w3,w7		
PA38	2§	F	2,11	60,w6	5,9,w52,w53	w3,w7	1	1
		M	2,33	38,58,w4	7,12,w52	w1		
PA39	3	F	11,26	13,38,w6	2,8,w52	w1	1	2
		M	11,33	58,75,w4,w6	14,12,w52	w1,w3,w7		
PA41	3	F	24,31	13,54,w4,w6	7,14,w52,w53	w1,w2	1	2
		M	24,2	60,48,w6	2	w1		
PA43	4	F	31,11	35,62,w6	2,14,w52	w1	2	2
		M	31,11	35,60,w4	9,w52,w53	†		
PA44	3	F	11	60,53,w4,w6	2,w52	w1,w3,w7	2	3
		M	33	60,58,w4	2,4,w53	w1,w3		
PA45	3	F	24,26	60,w6	4,9,w52,w53	w3	1	2
		M	2,11	46,58,w4	4,3,12,w52,w53	w3,w1,w2		
PA46	3	F	2,24	60,58,w4	3,9,w52,w53	w3,w2	2	3
		M	2,11	60,46,w6	4,w52,w53	w3,w7		
PA47	3	F	30,2	13,38,w4	2,7,w52,w53	w1	0	0
		M	24,11	60,w6	5,9,w53	w3		
PA48	4	F	11,2	46	3,4,w52	w3	1	2
		M	11,2	13,62,w4	2,w52	w3,w1		
PA49	3	F	24	48,60,w6	12,2,w52	w3,w7,w1	3	4
		M	24	48,46,7,w6	12,9,w52,w53	w3,w7		
PA50	3	F	24,33	60,w6	5,w52	w3	1	1
		M	24,2	38,55,w4,w6	12,w52,w53	†		
PA51	3	F	2	60	2,8,w52,w53	w3,w1	2	3
		M	2,11	60,62,w6	4,w52,w53	w3		
PA52	4	F	11,2	60,58,w4	12,3,w52	w3	3	4
		M	11	60,w6	12,1,w52	w3,w1		
PA53	5	F	11	13,27,w4	12,3,5,w52	w3	3	4
		M	11	13,55,w4	12,4,w52	w3,w1		
PA55	7‖	F	11,2	60,w6	2,14,w52	w1	1	1
		M	11,33	7,58,w4,w6	3,5,12,w52	w2,w3,w7		
PA57	4	F	2	54	4,12,w52	w1,w3	1	2
		M	2,33	55,7,w6	2,w52	w1		
PA58	4	F	24,2	62,50,w4,w6	3,w52	w1	0	0
		M	11	60,w6	9,12,w52,w53	w3		
PA59	3	F	11,24	54,w6	4,w53	w3	2	3
		M	11,2	62,38,w4	4,12	w3		
PA60	2	F	11,33	13,57,w4	2,1,12,w52,w53	w1,w3	2	3
		M	11,2	63,70	2,9,w53	w1,w3		
PA61	3‖	F	2	60	4,w53	w3	3	4
		M	2	60,62,w6	4,12,w53	w3		
PA63	3§	F	11,24	62,38,w6	2	w1,w3,w7	2	3
		M	11,31	62,51,w4,w6	5,13,w52,w53	w1,w3,w7		
PA65	4	F	24,2	57,62,w4,w6	12,3,w52	w3,w2	2	3
		M	24,11	35,46,55,w4,w6	12,14,w52	w3,w1		
PA66	3	F	11	55,62,w6	2,12,w52	w1,w3	1	2
		M	11,2	46,61,w6	4,14,w53	w1		

Table I—Cont'd

Patient			*HLA specificity*				*Number of loci with shared HLA antigens**	
No.	*No. of abortions*	*Sex*	*A*	*B*	*DR*	*DQ*	*ABDR*	*ABDRDQ*
PA67	3	F	11,26	46,61,w6	5,9,w52,w53	w1	2	3
		M	11,2	60,w6	2,9,w52	w1,w3		
PA68	3§	F	11	35,51,w4	4	w3	2	3
		M	11,24	46,55,w4,w6	4,12,w52	w3,w1		
PA69	3§	F	2	38,70	2,9,w52	w1,w3,w7	2	3
		M	2,11	60,75,w6	2,9,w52	w1,w3,w7		
PA70	3	F	33,2	58,60,w4,w6	12,w52,w53	w2,w1,w3	2	3
		M	33,24	58,46,w4	3,9,w52,w53	w2		
PA72	3	F	2,11	46,60,w6	4,w52	w3,w7	3	3
		M	2	46,54,w6	4,9,w52,w53	†		
PA73	3	F	24,31	60,w6	4,8,w52,w53	w3,w1,w6	1	2
		M	1,11	51,8,w4,w6	4,13,w52	w3,w4		
PA74	3	F	11,2	54,w6	4,12,w53	w3	1	2
		M	11,24	46,60,w6	9,w53	w3		
PA78	3	F	2,11	46,35,w6	5,2,w52	w3,w1	2	3
		M	2,11	46,14,w6	9,12,w52,w53	w3		
PA79	3	F	24,2	44,46,w4	7,w53	w1,w3	1	2
		M	24	60,w6	2,4,w53	w1,w3		
PA80	7	F	11,24	46,60,w6	9,12,w53	w3	1	2
		M	11	13,62,w6	4,7,w53	w3,w2		
PA81	3	F	33,11	44,55,w4,w6	12,14,w52	w1,w3,w6,w7	1	2
		M	33,2	67,58,39,w4,w6	2,3,w52	w1,w2,w6		
PA82	3	F	2	51,62,w4,w6	5,9,w52,w53	w3,w6,w2,w7	0	1
		M	24,11	35,60,w6	4,12,w53	w3		
PA83	4	F	2	75,60,w6	12,2,w52	w1,w6	3	3
		M	2,11	75,48,w6	12,14,w53	w3,w7		
PA84	3	F	11,33	53,58,w4	3,5,w52	w3,w2,w6	1	2
		M	11,24	54,w6	9,w52,w53	w3		
PA85	4	F	2	38,60,w6	14,8,w52	w3,w1,w7	1	2
		M	2	39,w4,w6	4	w3		
PA87	3	F	2,11	60,w6	9,14,w53	w1,w3	1	2
		M	2,24	35,46,w6	2,5,w52	w1,w3,w2,w7		
PA88	3	F	11	60,67,w6	2,5,w52	w1,w3	2	3
		M	11,2	13,38,w4	2,4	w1,w3		
PA89	4	F	11	13,60,w6	8,14,w52	w6,w1	0	1
		M	24,34	7,58,w4,w6	3,5,w52	w6,w2,w3		
PA90	3	F	2	46,38,w4,w6	2,14,w52	w6,w1	2	3
		M	2,24	46,39,w6	7,9,w53	w6,w2,w3		
PA91	3	F	11	60,51,w4,w6	12,2	w3,w1,w7	2	3
		M	33	60,13,w6	12,4,w53	w3		
PA92	3	F	2,11	37,39,w4,w6	4,8,w52,w53	w1,w3,w6	1	2
		M	2,33	56,58,w4,w6	3,14,w52	w1,w2,w6		
PA93	3	F	2	58,75,w4,w6	2,12,w52	w3,w1	2	3
		M	2,24	46,62,w6	4,12,w52,w53	w3		
PA94	3	F	2,11	60,w6	4,w53	w3,w4,w6	2	3
		M	2,24	46,48,w6	4,w53	w3,w4,w6		
PA95	3	F	2,24	51,60,w4,w6	12,14,w52,w53	w1,w3,w7	1	2
		M	2,11	35,46,w6	5,8,w52	w1,w3,w7		
PA96	6	F	2,11	52,38,w4	5,2,w52	w1,w3	2	3
		M	2,24	14,46,w6	5,1,w52	w1,w3,w4,w6,w7		
PA97	3	F	11,24	51,13,w4	2,5,w52	w1,w3,w6,w7	1	2
		M	11	39,56,w6	7,w53	w1,w2		
PA98	4	F	11	46,35,w6	8,4,w52,w53	w7,w6	1	2
		M	2	62,47	8,5,w52	w7,w4		
PA99	5	F	24	46,62,w6	9,8	w3,w1	1	2
		M	24	55,60,w6	4,w52	w3,w4		
PA100	3	F	2	39,w4,w6	2,9,w53	w1,w3	2	3
		M	2,11	13,46,w4	2,9,w53	w1,w3,w6		
PA101	6	F	11	51,54,w4,w6	2,5,w52	w1,w3	1	2
		M	2	60,46,w6	2,8,w52	w1,w6		
PA102	3	F	11,3	35,75,w6	12,2,w52	w3,w6,w4	2	3
		M	11,2	38,46,w4,w6	12,3,w52	w3,w6,w1		

these studies provide further evidence for our hypothesis that major histocompatibility complex–linked recessive genes affect both fetal viability and susceptibility to cancer.

Material and methods

All of the patients used in this study were from the Obstetrics Clinic of the National Taiwan University Hospital. None of the women with recurrent spontaneous abortions had any anatomical, chromosomal, or hormonal abnormalities; infectious diseases; or lupus anticoagulant, antinuclear antibodies, or anticardiolipin antibodies. The husbands all had normal semen analyses. The primary aborters had three or more consecutive spontaneous abortions and no live births. The secondary aborters had one or more live births and then three or more consecutive spontaneous abortions. The normal fertile controls matched for age with the patient population had two or more live births and did not have a history of spontaneous or induced abortions.

The HLA typing was done by the microcytotoxicity test with reagents calibrated against the standard antisera previously described.[9] Because of the high prevalence of HLA-Bw4,Bw6 and HLA-DRw52,DRw53 in the population, these antigens were not used in determining antigen sharing. The typing for HLA-C was done both in the patients with recurrent spontaneous abortions and in the patients with gestational trophoblastic tumors reported previously[8] because of the recent report[10] that there are HLA-C–like antigens in several cultured choriocarcinoma cell lines and the possibility exists that such a "nonclassical" class I major histocompatibility complex antigen could be involved the genetic basis of fetal losses and cancer. The significance of the HLA antigen sharing was determined by the χ^2 test with the use of a 2 by 2 contingency table, and $p < 0.05$ was taken as the level of significance.

All the sera used for antibody and mixed lymphocyte reaction blocking activity were taken for analysis after the last pregnancy recorded in the various groups of patients. The maternal antipaternal lymphocytotoxic antibodies were determined by the microlymphocytotoxicity assay with the use of rabbit complement.[11] The husband's lymphocytes were separated into T and B cells on a nylon wool column and then resuspended in Roswell Park Memorial Institute 1640 medium (3×10^6 cells/ml). Each cell type was tested separately, and the results were the same. Deactivated maternal serum was added in doubling dilutions to 1 μl of the husband's cells in the microtiter plates, and the assays were performed in triplicate. The reaction mixture was incubated at 37° C or 4° C for 1 hour, complement was added and the mixture was incubated for another hour. Eosin and formalin were added, and the plates were examined microscopically. Cytotoxicity ≥30% was considered to be a positive reaction.

The mixed lymphocyte reaction–blocking activity[12, 13] was measured with lymphocytes prepared from heparinized peripheral blood by Ficoll-Hypaque gradient centrifugation. The husband's lymphocytes (stimulator cells) were treated with 50 μg/ml mitomycin C for 30 minutes at 37° C and then washed three times with Roswell Park Memorial Institute 1640 medium. Cultures were set up in triplicate in flat-bottom microtiter plates (Nunc 63320 U96, Rockilde, Denmark) with 1×10^5 maternal (responder) and 1×10^5 paternal (stimulator) lymphocytes in 200 μl of Roswell Park Memorial Institute 1640 medium containing either 20% inactivated pooled male AB sera (control) or 20% inactivated maternal (test) serum. The cultures were incubated in a humidified incubator containing 5% carbon dioxide at 37° C for 6 days. After 18 hours' incubation with tritiated thymidine (0.5 μCi/well), the cells were harvested on a glass fiber filter, the filters were counted in a liquid scintillation counter, and the results were expressed as the mean counts per minute. The percentage blocking by the maternal serum was calculated as:

$$\left(1 - \frac{\text{Mean cpm test cells}}{\text{Mean cpm control cells}}\right) \times 100$$

where *cpm* is counts per minute. Blocking of the mixed lymphocyte reaction ≥20% was considered to be indicative of the presence of blocking factor in the serum.

Results

The HLA typing was performed on 91 couples with primary recurrent spontaneous abortions (Table I) and on 32 couples with secondary recurrent spontaneous abortions (Table II). Twenty-nine normal fertile couples were also typed (Table III), and their data were added to those of the 22 normal couples previously reported[8] to give a total normal population of 51 couples. These three groups of patients (Table IV), the previously reported 22 normal fertile couples,[8] and the 26 couples in whom the woman had a gestational trophoblastic tumor[8] were also typed for their HLA-C antigens (Table IV).

Maternal antipaternal cytotoxic antibodies and mixed lymphocyte reaction blocking factor were determined in 70 of 91 primary aborting couples and in 29 of the 32 secondary aborting couples (Table V). There was no correlation between HLA sharing and the production of cytotoxic antibodies or between HLA sharing and the presence of mixed lymphocyte reaction blocking factor in either of the aborting groups or in normal fertile couples.

The HLA sharing in both primary and secondary spontaneous aborters was greater than that in normal fertile couples, but the pattern of sharing was different (Table VI). The primary aborters shared HLA-A, HLA-DQ, and three or more of the HLA-A, B, DR,

Table II. HLA typing of the couples with secondary recurrent spontaneous abortions

Patient				*HLA specificity*				*Number of loci with shared HLA antigens**	
No.	*Live born*	*Spontaneous abortion*	*Sex*	*A*	*B*	*DR*	*DQ*	*ABDR*	*ABDRDQ*
SA1	1	4	F	11,33	58,w4,w6	2,3,w52	w1,w2	1	1
			M	11,2	75,w6	12,14,w52	w3,w7		
SA2	1	3	F	11,2	60,75,w6	2	w1	2	2
			M	11,23	60,w6	4,12,w52,w53	†		
SA3	1	4	F	11,31	62,54,w6	4,w53	w3	2	3
			M	11,33	62,60,w4,w6	14,w52,w53	w3,w1		
SA4	1	2	F	11,24	54,60,w6	4,w53	w3	2	3
			M	11,1	56,62,w6	4	w3		
SA5	1	4	F	11,2	38,75,w6	8,12,w52	w3,w7,w1	1	2
			M	11,24	46,60,w6	5,9,w52	w3,w7		
SA6	1	3	F	24,26	60,w6	5,w52	w3,w7	2	2
			M	24,11	60,35,w6	2,4,w53	w1		
SA7	1	3	F	24,1	37,60,w4,w6	14,w52,w53	w1	0	0
			M	11	13,51,w4	9,w52,w53	w3,w7		
SA8	1	3	F	11,2	46,75,w6	9,12,w52,w53	w3,w7	1	1
			M	11,24	60,w6	4,w52	w1		
SA9	1	3	F	34	58,53,w4	3,w52	†	1	1
			M	33,31	58,52,w4	2,7,w52,w53	w1,w4,w7		
SA10	1	5	F	24,33	13,27,w4	2,3,w52	w1,w2	2	3
			M	24,11	48,58,w4,w6	2	w1		
SA11	1	4	F	11,24	13,27,w4	12,w52	w3,w7	3	4
			M	11	13,7,w6	12,2,w52	w3,w1		
SA12	1	3	F	24,2	13,61,w6	12,w52	w3,w7	3	4
			M	24,2	13,w6	12,14,w52	w3,w1		
SA13	1	3	F	2,11	13,75,w4,w6	2,w52	w1,w6	2	3
			M	2,33	46,62,w6	2,9,w53	w1,w6,w3		
SA14	1	3	F	11,2	46,39,w6	12,w52	w3,w7	2	3
			M	11,31	46,70	14,w52	w3,w7		
SA15	1	3	F	2	46,60,w6	12,w52	w3	0	0
			M	11,33	57,75,w4,w6	8,w52,w53	w1		
SA16	1	4	F	24,2	75,46,w6	9,12,w52,w53	w3,w7	2	3
			M	11	75,60,w6	9,12,w52,w53	w3,w7		
SA17	2	6	F	11	35,63,w6	1,2	w1	1	1
			M	11,33	58,60,w4,w6	3,9,w52,w53	w2,w3		
SA18	1	5	F	24,31	60,w6	9,w52	w1,w3,w7	1	2
			M	11,2	60,35,w6	1,5,w52	w1,w3,w7		
SA19	1	2	F	2,33	58,60,w4,w6	3,w52	w2,w3	2	2
			M	2,33	58,61,w4,w6	2,6,w52	w6,w1		
SA21	2	3	F	11,2	46,60	8,9,w52,w53	w3,w1	2	3
			M	11	46,62,w6	4,7,w53	w3		
SA22	1	4	F	2,24	27,w4	2,5,12,w52	w1,w3	2	3
			M	2,24	60	2	w1		
SA23	2	2	F	31	13,75,w6	7,12,w53	w2,w3,w7	1	1
			M	2,11	13,55,w6	2,8	w1,w6		
SA25	1	3	F	11,24	61,27,w4,w6	9,4,12,w52,w53	w3	2	3
			M	11,24	55,60	9,2,w53	w3,w1		
SA26	1	3	F	11,2	60,w4,w6	9,10,w53	w1,w6	2	2
			M	11,24	60,55,w6	5,12,w52	w2,w3		
SA27	1	2	F	24,2	60,w6	12,4,w52,w53	w3	1	2
			M	11	27,62,w4,w6	12,w52,w53	w3,w1		
SA28	2	7	F	26,32	60,27,w4,w6	9,12,w52,w53	w2,w3,w6	2	3
			M	24	60,46,w4,w6	9,12,w53	w2,w3,w6		
SA29	1	4	F	11,33	58,75,w4,w6	2,3,w52	w1,w2	1	2
			M	2,24	51,62,w4,w6	2,4,w53	w1,w3		
SA31	4	‡	F	2,24	13,54,w6	12,w52	w3,w7	0	1
			M	11,26	35,60	9,w53	w3		
SA32	1	4	F	2	60,w6	14,12,w52	w1,w3	3	4
			M	2,29	60,46,w6	14,w52	w1		
SA33	1	4§	F	33,26	8,58,w4,w6	3,w52	w2	2	3
			M	33,24	60,w6	3,9,w52,w53	w2,w3		
SA34	1	3	F	24,11	60,62,w6	5,4,w52,w53	w3	2	3
			M	24	38,51,w4,w6	5,12,w52	w3,w7		
SA35	1	3	F	11,26	13,52,w4	12,4,w52,w53	w3,w6,w7	2	3
			M	11	27,60,w4,w6	12,5,w52	w3,w6		

*Exclusive of Bw4,Bw6 and DRw52,DRw53.
†Blank; therefore, it is different from the other DQ antigen typed.
‡Intrauterine fetal death twice and three neonatal deaths (all within 3 weeks; cause unknown).
§Intrauterine fetal death once and one neonatal death.

Table III. HLA typing of normally fertile couples

Patient			*HLA specificity*				*Number of loci with shared HLA antigens**	
No.	*No. of children*	*Sex*	*A*	*B*	*DR*	*DQ*	*ABDR*	*ABDRQ*
N17	2	F	23,11	60,w6	4,14,w52,w53	w3,w1	1	2
		M	2	38,w6	4,w52	w3		
N24	4	F	11	13,57,w4	12,4,w52	w3	2	3
		M	11,2	55,60	12,5,w52	w3		
N25	3	F	11	60,w6	2,12,w52	w3,w1	0	1
		M	33,2	58,46,w4	3,4,w52	w3,w2		
N26	2	F	24,11	60	4,9,w52	w3	1	1
		M	2	60	2	w1		
N27	3	F	11	62	4,5,w52,w53	w3	1	2
		M	11,2	46,38,w4	9,12,w53	w3,w1		
N28	2	F	24,11	39,13,w4,w6	5,9,w52,w53	w3	2	3
		M	24	55,60,w4,w6	5,3,w52	w3,w2		
N29	2	F	11,1	51,37,w4	12,w53	w3,w7	1	1
		M	11	62,39,w6	4,9,w53	†		
N30	3	F	11	51,60,w4,w6	2,5,w52	w7,w1,w3	1	2
		M	11	75,58,w4,w6	9,12,w53	w7		
N31	3	F	24,11	27,60,w4,w6	7,9,12,w52	w2,w3,w7	0	1
		M	26	39,w6	8,w52	w1,w3		
N32	2	F	11,2	46	4,14,w52,w53	w1,w2,w3,w7	3	4
		M	11,24	46,55,w6	5,14,w52	w1,w3,w7		
N33	2	F	33	60,58,w4,w6	2,14,w52	w1	1	1
		M	31,11	60,w4,w6	9,w52,w53	w3,w7		
N34	3	F	11	62,60,w6	2,12	w1,w3,w7	0	1
		M	24,2	55,61,w6	9,14,w52,w53	w1,w3		
N35	3	F	2,11	38,w4,w6	12,w52	w3,w7	2	2
		M	2	46,w6	12,14,w52	w1		
N36	3	F	11	60,w6	4,2,w52,w53	w1,w3	2	3
		M	11,2	52,39,w4,w6	4,8,w52,w53	w1		
N37	2	F	2,24	58,53,w4	5,w52	w3	1	1
		M	2,11	13,38,w4	2,14,w52	w1		
N38	3	F	2,33	51,58,w4	3,12,w52	w2,w3,w7	1	2
		M	11	60,46,w4,w6	3,12,w52	w2,w3,w7		
N39	3	F	2,33	58,52,w4	2,4,w53	w1,w3	1	2
		M	2,24	60,48,w6	3,9,w52,w53	w2,w3		
N40	3	F	2	62,38	5,12,w52	w3,w7	2	3
		M	26,11	62,w6	5,w52	w3		
N41	3	F	11,2	60,w6	4,w53	w2,w3	2	2
		M	11	60,13,w6	2,12,w52	w1		
N42	2	F	2,11	60,51,w4,w6	4,9,w53	†	2	2
		M	2,11	60,38,48,w6	12,w52	w3		
N43	2	F	11	51,62,w4,w6	4,9,w53	w1,w3	0	1
		M	33,2	38,58,w4	14,w53	w1		
N45	2	F	2,26	13,60,w6	5,12,w52	w3,w7	1	1
		M	2,33	51,58	8,w52	w1,w6		
N46	2	F	2,11	60,39,w6	12,w52	w2,w1,w6	3	4
		M	2,33	60,46,w6	12,7	w2,w3		
N47	3	F	24,11	7,35,w6	4,w53	w3	1	2
		M	24	38,54,w4	2,12,w52	w3,w1		
N48	2	F	24	60,54,w6	4,w53	w4	1	1
		M	2,11	60,38,w6	5,w52	w3,w7		
N49	2	F	24,31	60,46,w6	9,w53	w3,w4,w6	0	1
		M	11,33	57,75,w4,w6	3,12,w52	w3,w2,w7		
N50	3	F	11,2	48,60,w6	4,12,w52	w3,w7	1	1
		M	11,24	58,75,w4,w6	2,14,w52	w1		
N51	5	F	2,11	51,46,w4,w6	4,9,w53	w3,w6	0	1
		M	24,33	62,57,w4,w6	3,12,w52	w3,w2,w7		
N52	2	F	24,11	51,54,w4,w6	4,w52,w53	w3,w4,w6	0	1
		M	2,33	60,w6	2,12	w3,w1,w6		

*Exclusive of Bw4,Bw6 and DRw52,DRw53.

†Blank; therefore, it is different from the other DQ antigen typed.

and DQ antigens; whereas the secondary aborters did not have an excess of sharing at any one locus but did share to a significantly greater extent two or more of the HLA-A, B, and DR antigens and three or more of the HLA-A, B, DR, and DQ antigens. The sharing pattern in the couples in whom a gestational trophoblastic tumor developed in the woman more closely resembled that in the primary aborters: they shared HLA-B, HLA-DQ, and three or more of the HLA-A, B, DR, and DQ antigens. There was no significant difference in cytotoxic antibody formation between those couples with normal fertility and those with primary or secondary spontaneous abortions (Table VI). Fewer primary aborters had a significant level of mixed lymphocyte reaction blocking factor in their sera than did the secondary aborters, and the latter did not differ significantly from normal fertile couples (Table VI).

Comment

The same large, ethnically homogeneous Chinese population in Taiwan was examined for HLA sharing in couples with primary or secondary recurrent spontaneous abortions, in couples in whom the woman had a gestational trophoblastic tumor,[8, 14] and in normal fertile couples. There was significant HLA sharing in excess of that seen in normal fertile couples in all three disease groups, and the feature common to all was sharing three or more of the HLA-A, B, DR, and DQ antigens.

The observation that sharing three or more HLA antigens was the primary pattern suggests that sharing the segment of the chromosome that carries the major histocompatibility complex is critical and not the sharing of antigens at a specific HLA locus. This conclusion is consistent with the one drawn from pooled HLA sharing data,[1, 2] and it supports our hypothesis that major histocompatibility complex—linked recessive genes are involved in recurrent fetal losses and in susceptibility to cancer.[4, 5, 8] This hypothesis is all the more cogent now because all the data in our studies were generated from the same large, ethnically homogeneous population. The difference in the pattern of HLA antigen sharing between primary and secondary recurrent spontaneous aborters suggests that there may be a somewhat different genetic basis for the two types of pregnancy loss.

The antibody responses observed in this study may be interpreted in the light of our recent experimental embryo transfer studies in allogeneic matings involving the WF (*u* haplotype) and DA (*a* haplotype) strains of rats.[15] There are two types of major histocompatibility complex histocompatibility antigens in the DA strain: the major allele-specific class I transplantation antigen A^a and the pregnancy-associated class I antigen Pa that carries only broadly shared antigenic determinants. Both antigens are synthesized in the trophoblast cells, but only the Pa antigen is expressed on the surface of the trophoblast cells in the WF (female) and DA (male) mating and the antibody response to it does not affect the heterozygous fetuses. However, when a DA and DA homozygous embryo is transferred to a pseudopregnant WF female, there is an antibody response to the A^a transplantation antigen as well as to the Pa antigen, but the anti-A^a antibody is not deleterious: the pregnancy develops normally and produces normal offspring. However, in some transfers the DA homozygous embryos die and are resorbed. In this situation, only anti-Pa antibodies are formed, as in the natural mating. These findings suggest that the anti-Pa antibodies are elicited first and that the anti-A^a antibodies appear later, depending on the amount of antigen to which the maternal immune system is exposed.

In the human pregnancy, the mixed lymphocyte reaction blocking factor, which is presumably an antibody, may be analogous to the anti-Pa antibody, and the antipaternal cytotoxic antibodies may be analogous to the anti-A^a antibodies. In the normal situation, the antigenic stimulus of several term pregnancies elicits the highest response because approximately three fourths of normal pregnancies had mixed lymphocyte reaction blocking factor. In the secondary aborters, the one or two pregnancies that were carried to term before the onset of recurrent fetal losses would provide a similar, but less potent, stimulation. This interpretation is consistent with the presence of mixed lymphocyte reaction blocking factor in the sera of approximately one half the secondary aborters. Finally, the primary aborters would be exposed to a minimal antigenic stimulus because they would not have carried any pregnancies to term, and they should have the lowest level of mixed lymphocyte reaction blocking factor. They do; only one fourth of them had it. In this interpretation then, the presence of mixed lymphocyte reaction blocking factor would reflect the type of pregnancy rather than determine it. The antipaternal cytotoxic antibodies are the antibodies to the allele-specific class I antigens and are the tissue-typing reagents in both species.

In summary, HLA sharing occurs in significant excess of normal in couples with primary or secondary recurrent spontaneous abortions and in couples in whom a gestational trophoblastic tumor develops in the woman. This observation supports the hypothesis about the genetic cause of these defects, at least in certain populations; several other well-defined populations should be tested to extend explicitly this generalization.

Table IV. HLA-C typing of couples with recurrent spontaneous abortions and of normally fertile couples

Patient	*Sex*	*C*	*Patient*	*Sex*	*C*	*Patient*	*Sex*	*C*	*Patient*	*Sex*	*C*
Primary recurrent spontaneous abortions											
PA1	F	w7	PA2	F	*	PA3	F	w3	PA4	F	*
	M	*		M	*		M	w4		M	*
PA5	F	w3	PA6	F	w1	PA7	F	w7	PA8	F	w7
	M	w1		M	w1,w3		M	*		M	w1
PA9	F	w1,w3	PA10	F	w3	PA11	F	w7	PA12	F	w3
	M	w1,w3		M	*		M	*		M	w7
PA13	F	*	PA14	F	w3	PA15	F	w3	PA16	F	w6
	M	*		M	*		M	w1		M	w6,w3
PA17	F	w4,w7	PA18	F	*	PA19	F	w1,w3	PA20	F	w7
	M	w1		M	*		M	w1,w3		M	w3
PA21	F	*	PA22	F	w3,w1	PA23	F	w3,w6	PA24	F	w7
	M	*		M	w3		M	w7		M	w1,w3
PA25	F	w7	PA26	F	*	PA27	F	*	PA28	F	w4
	M	w1		M	w3		M	w1,w3		M	w6
PA29	F	*	PA30	F	w1	PA31	F	w1	PA32	F	*
	M	*		M	w1		M	w6		M	w1
PA33	F	*	PA34	F	*	PA35	F	*	PA36	F	w1,w6
	M	w1		M	w1		M	*		M	w1,w3
PA37	F	w3,w7	PA38	F	w3	PA39	F	w3,w7	PA41	F	w1,w6
	M	w3,w1		M	w3,w7		M	*		M	w7
PA43	F	w3	PA44	F	*	PA45	F	w7	PA46	F	w3
	M	w3,w7		M	w3		M	w3		M	w3,w1,w7
PA47	F	w6	PA48	F	w3	PA49	F	w7	PA50	F	w3
	M	w4		M	w3,w1		M	w7		M	w3,w7
PA51	F	*	PA52	F	*	PA53	F	*	PA55	F	w7
	M	w4		M	*		M	*		M	w7
PA57	F	w1	PA58	F	w6	PA59	F	w1,w2	PA60	F	*
	M	*		M	*		M	w4		M	w1,w3
PA61	F	w4,w3	PA63	F	w6,w7	PA65	F	w3	PA66	F	w1
	M	w4,w1		M	*		M	w3,w1		M	w1,w3
PA67	F	w1,w3	PA68	F	w3	PA69	F	w7	PA70	F	w3
	M	w7		M	w3,w1		M	w7		M	w3,w1
PA72	F	w7	PA73	F	w1,w7	PA74	F	w1	PA78	F	w1,w3
	M	w1,w3		M	*		M	w1,w3,w7		M	*
PA79	F	w1,w3,w7	PA80	F	w1,w3	PA81	F	w3	PA82	F	w3
	M	w1,w3		M	w4		M	w3,w1		M	w3
PA83	F	w3	PA84	F	w3	PA85	F	w7	PA87	F	w1,w3,w7
	M	*		M	w1		M	w7		M	w1,w3
PA88	F	w7	PA89	F	w3,w7	PA90	F	w1,w3,w6	PA91	F	*
	M	w7,w3		M	w3,w7		M	w1,w3,w7		M	w3,w7
PA92	F	*	PA93	F	w3,w1	PA94	F	w3,w7	PA95	F	w3
	M	w1,w3		M	w3		M	w3,w1		M	w3,w1,w7
PA96	F	w7	PA97	F	w3	PA98	F	w4,w1,w3	PA99	F	w3,w1
	M	w1,w3		M	w1		M	w4		M	w3
PA100	F	w7	PA101	F	*	PA102	F	w4			
	M	w1,w3		M	w1,w3,w6		M	w7			
Secondary recurrent spontaneous abortions											
SA1	F	w3	SA2	F	*	SA3	F	w1,w4	SA4	F	w1
	M	w1		M	w7		M	w3,w7		M	w1
SA5	F	w7	SA6	F	w3	SA7	F	w6	SA8	F	w3
	M	w1		M	w3,w7		M	w3		M	w3,w7
SA9	F	w3	SA10	F	w3	SA11	F	w3	SA12	F	w3
	M	w3		M	w3		M	w3		M	w3
SA13	F	*	SA14	F	w1,w3	SA15	F	w3,w1	SA16	F	w1,w3
	M	w1,w3		M	w1,w3		M	w3		M	*
SA17	F	w4	SA18	F	w6,w7	SA19	F	w3,w7	SA21	F	w1
	M	w7		M	w4		M	w3		M	w3
SA22	F	w6	SA23	F	w6	SA25	F	w3	SA26	F	w7
	M	*		M	w3		M	w3,w1		M	w1,w3
SA27	F	w7	SA28	F	*	SA29	F	w3	SA31	F	w1
	M	w1		M	w1,w3		M	*		M	w3
SA32	F	w3	SA33	F	w3,w7	SA34	F	w7,w1	SA35	F	w3
	M	w3,w1		M	w3		M	w7		M	w3

Table IV—Cont'd

Patient	*Sex*	*C*	*Patient*	*Sex*	*C*	*Patient*	*Sex*	*C*	*Patient*	*Sex*	*C*
Gestational trophoblastic tumors											
T1	F	w7	T2	F	w3,w1	T3	F	*	T4	F	w3
	M	w3		M	w3,w4		M	w7		M	w3
T5	F	w3	T6	F	w3	T7	F	w7	T8	F	*
	M	*		M	w4		M	w3		M	w7
T9	F	w1,w3	T10	F	w3,w7	T11	F	w3,w7	T13	F	w1,w3
	M	w1		M	w3,w1		M	w3		M	*
T14	F	w1	T15	F	w1,w3	T16	F	w3,w1	T18	F	w3
	M	w1,w3		M	w1,w3		M	w3		M	w7
T19	F	w3	T20	F	w3,w1	T21	F	w1,w3	T22	F	*
	M	w3,w1		M	w3		M	w7		M	w1,w6
T23	F	w3,w7	T24	F	w3	T25	F	w3	T26	F	w3
	M	w3,w7		M	w3,w1		M	w6,w7		M	w7
T27	F	w3	T28	F	w3						
	M	w3		M	w7						
Normal fertile couples											
N1	F	w3	N2	F	w3	N3	F	w4	N4	F	w1,w3
	M	*		M	w3,w1		M	w1,w3		M	w6
N5	F	*	N6	F	w1,w3	N7	F	w1,w3	N8	F	w1,w3
	M	w1,w3		M	w1,w3		M	*		M	w4,w3
N9	F	w3	N10	F	w1	N11	F	w1,w3,w4	N12	F	w1,w3
	M	w3,w1		M	w3		M	w1		M	w1,w3
N13	F	w3	N14	F	w6,w1,w3	N15	F	w4	N16	F	*
	M	*		M	w6		M	w1		M	*
N17	F	w7	N18	F	w3	N19	F	*	N20	F	*
	M	w7		M	w7		M	w1		M	w1
N21	F	w3	N22	F	w7	N23	F	w4	N24	F	*
	M	w3		M	w3		M	*		M	*
N25	F	*	N26	F	*	N27	F	w4	N28	F	w3,w7
	M	w1		M	*		M	w1		M	*
N29	F	w6	N30	F	w3	N31	F	*	N32	F	w3
	M	w4,w7		M	w3		M	w7		M	w3,w1
N33	F	w3	N34	F	w3	N35	F	w1,w3	N36	F	w7
	M	w3		M	w3		M	w7		M	w7
N37	F	w7	N38	F	w1,w3	N39	F	*	N40	F	w3
	M	w3		M	*		M	w3		M	*
N41	F	w7	N42	F	*	N43	F	w4	N45	F	w3,w7
	M	w3		M	w4,w7		M	w3,w7		M	*
N46	F	w7	N47	F	w1	N48	F	w1	N49	F	w3,w1
	M	w7,w1,w3		M	w3		M	w7		M	w3
N50	F	*	N51	F	w1,w3	N52	F	w1,w3			
	M	w1,w3		M	w1,w7		M	w1,w7			

*Blank.

Whereas the pattern of HLA antigen sharing may differ in each of the disease groups, all of them share three or more of the HLA-A, B, DR, and DQ antigens, and this observation suggests that recessive loci in the major histocompatibility complex region of the chromsome other than the HLA loci themselves play a major role in the cause of recurrent spontaneous abortions and of gestational trophoblastic tumors.

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Table V. Maternal antibody response to paternal antigens in pregnancy*

Population		*Complement-dependent antipaternal cytotoxic antibodies†*						*Mixed lymphocyte reaction inhibiting factor†*					
		Total		*0-1 HLA match*		*2 HLA match*	*≥3 HLA match*	*Total*		*0-1 HLA match*		*2 HLA match*	*≥3 HLA match*
Status	*Total no.*	*No.*	*%*	*(no.)*	*HLA/Ab concurrence‡*	*(no.)*	*(no.)*	*No.*	*%*	*(no.)*	*HLA/Ab concurrence‡*	*(no.)*	*(no.)*
Normal	51	4	7.8	2	+	2	0	38	74.5	18	+	12	8
					−	15	11				−	5	3
Primary aborters	70	4	5.7	2	+	1	1	20	28.5	6	+	6	8
					−	29	27				−	24	20
Secondary aborters	29	6	20.7	0	+	1	5	16	55.2	4	+	3	9
					−	6	10				−	4	6

The difference between the total number of patients and the number listed under each category is the number of patients with 0 to 1 HLA match and no antibody or no mixed lymphocyte reaction inhibiting factor, respectively.

*Serum tested after the number of pregnancies shown in Tables I to III.

†Cytotoxicity ≥30% and mixed lymphocyte reaction inhibition ≥20% were considered to be positive reactions.

‡+, HLA antigen match and presence of antibody coincide; −, they do not coincide.

Table VI. The sharings of HLA antigens in the couples in whom the woman has recurrent spontaneous abortions

	Normal fertile couples		*Recurrent spontaneous abortions*		*Gestational trophoblastic tumors**
	No.	*%*	*Primary*	*Secondary*	
A	28/51	54.9	68/91 (74.7%) $p < 0.02$	22/32 (68.8%) NS†	15/26 (57.7%) NS†
C	18/51	35.3	35/91 (38.4%) NS	15/32 (46.9%) NS	13/26 (50.0%) NS
B	14/51	27.4	24/91 (26.3%) NS	15/32 (46.9%) NS	14/26 (53.8%) $p < 0.04$
DR	18/51	35.2	43/91 (47.2%) NS	15/32 (46.9%) NS	12/26 (46.2%) NS
DQ	29/51	56.8	74/91 (81.3%) $p < 0.0001$	21/32 (65.6%) NS	22/26 (84.6%) $p < 0.02$
ABDR ≥ 2	19/51	37.2	44/91 (48.3%) NS	20/32 (62.5%) $p < 0.04$	14/26 (53.8%) NS
ABDRDQ ≥ 3	11/51	21.5	38/91 (41.7%) $p < 0.02$	16/32 (50%) $p < 0.01$	13/26 (50.0%) $p < 0.02$
Cytotoxic antibody	4/51	7.8	4/70 (5.7%) NS	6/29 (20.7%) NS	
Blocking factor	38/51	74.5	20/70 (28.5%) $p < 0.0001$	16/29 (55.2%) NS	

*References: 8, 13, Table IV of this article.

†*NS*, Not significant. $p < 0.05$ Is significant compared with normally fertile couples. X^2 test was used for the analysis of significance.

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Studies of the spontaneous motility and the effect of histamine on isolated myometrial strips of the nonpregnant human uterus: The influence of various uterine abnormalities

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We investigated the spontaneous uterine activity of isolated corpus uteri myometrial strips from 30 patients with nonpathologic myometrium, 26 patients with uterine myoma, 23 patients with uterine adenomyosis, and three patients with uterine malignancy. We also investigated the influence of these conditions on the response of the uterus to histamine. The results show the same qualitative cyclic changes of the spontaneous motility of isolated myometrial strips throughout the menstrual cycle in all the abnormalities studied. These changes are characterized by a low amplitude and high frequency of spontaneous contractions in the proliferative phase and lower frequency with higher amplitude of contractions in the secretory phase. The isolated strips from patients with myomas present the highest spontaneous activity in reproductive age and preclimacteric women, but not in menopausal women. Histamine produced concentration-related contractions that are not significantly different in all the myometrial strips studied. (Am J Obstet Gynecol 1990;163:189-95.)

Key words: Isolated human uterus, histamine, uterine motility

It has been reported that the spontaneous motility of isolated muscular strips of the human uterus varies widely, with sexual phase, anatomic origin of the strip, pregnancy, and the experimental conditions used.[1-3] Moreover, several authors have shown that there are wide variations in the frequency and force of contractions, as well as the response to drugs, of human myometrial strips from different uteri, although the cause of these large variations is still obscure.[3-5] Conversely, many studies of the isolated human uterus have been done with no consideration for the clinical diagnosis in each case; therefore the uterine abnormality of the women who had operations could be a source of the variation in the results described.

In this investigation we studied the spontaneous uterine activity of isolated myometrial strips from patients with various uterine pathologic conditions and investigated the influence of those pathologic conditions on the response of the corpus uteri to histamine.

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Material and methods

Myometrial tissue was obtained from 82 women undergoing hysterectomy because of various gynecologic pathologic conditions. A sample of each uterus obtained was sent for histologic examination to check the pathologic diagnosis and the phase of menstrual cycle. The specimens were divided on the basis of their final diagnosis as follows: group 1: 30 patients who underwent hysterectomy for gynecologic conditions that did not affect the uterus served as normal control subjects; group 2: 26 patients with uterine myoma; group 3: 23 patients with uterine adenomyosis; and group 4: three patients with uterine malignancy.

Since it has been reported that menopause and the phase of the sexual cycle may influence uterine motility, subjects were then separated into subgroups according to the classification used by Sandberg et al.[1] as follows: proliferative group, 18 patients aged 29 to 51; secretory group, 20 patients aged 37 to 53; preclimateric group, 13 patients aged 41 to 57; and menopausal group, 31 patients aged 52 to 78.

Isolated strips of uterus. Immediately after abdominal hysterectomy, muscle strips from an intermediate layer were cut longitudinally from the anterior part of the corpus of the uteri. The tissue was rapidly immersed in a Jalon solution of the following composition: sodium chloride 155.17 mmol/L, potassium chloride

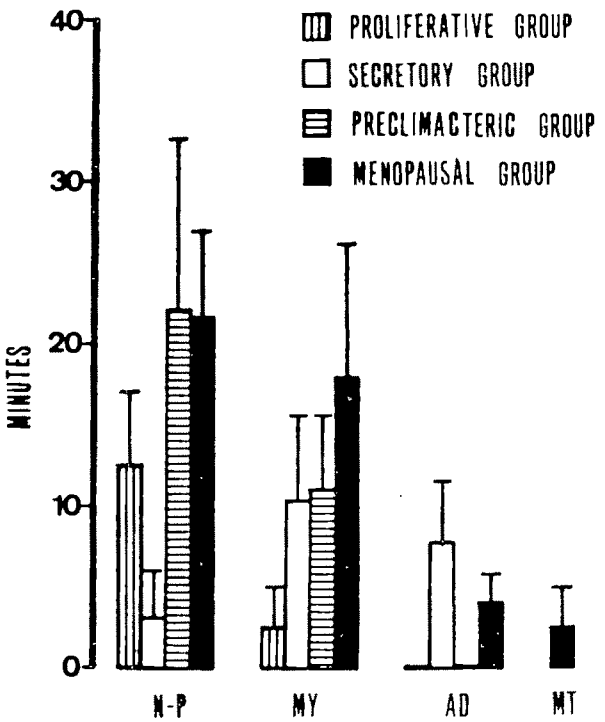


Fig. 1. Time in minutes for myometrial strips to start spontaneous motility. Strips were taken from uteri with nonpathologic conditions *(N-P)* (n = 46), myomas *(MY)* (n = 39), adenomyosis *(AD)* (n = 25), and malignant tumors *(MT)* (n = 5). Each value is the mean ± SEM.

5.68 mmol/L, calcium chloride 0.41 mmol/L, sodium bicarbonate 5.95 mmol/L, glucose 2.78 mmol/L; samples were then transported to the laboratory. The tissue samples were stored at 4° C until the next day. Muscle strips measuring approximately 2 × 3 × 35 mm were dissected and then mounted in a 20 ml organ bath containing Jalon solution at 31° C and were continuously gassed with 95% oxygen and 5% carbon dioxide. Isometric tension was recorded by a Ugo Basile C40 7010 transducer (Milan, Italy) connected to a Ugo Basile mod Gemini 7070 recorder. Initial tension was set at 1 gm and the preparations were undisturbed for 1 hour before any drugs were added. At the end of this period the concentration-response curve to histamine was obtained by cumulatively adding the drug at increments of 1 log unit. Only one complete dose-response curve to histamine was constructed for each myometrial strip because tachyphylaxis to histamine has been reported for the rat uterus.[6, 7]

Immediately after completion of the pharmacomechanical studies, the tissue was removed from the bath, heated for 24 hours, and then weighed on a precision balance.

Analysis of data. The spontaneous activity of the muscle strips developed in these experimental conditions was evaluated as described previously[7] in terms of (1) isometric tension, (2) frequency of contraction, (3) functional activity, and (4) period of time necessary for the tissues to develop spontaneous activity.

The values for the isometric tension developed (expressed in milligrams of force per milligram of tissue dry weight) were obtained by calculating the mean amplitude of all the contractions recorded in a 10-minute interval. The frequency of contractions represents the number of contractions in the same period of time, and functional activity corresponds to the product of these two parameters expressed in arbitrary units. The period of time before the beginning of spontaneous uterine activity is expressed in minutes.

The responses of the tissue resulting from the addition of histamine were directly determined as changes in isometric tension and transformed into tension (i.e., force per gram of tissue dry weight). The 50% effective concentration (EC_{50}) was calculated graphically from a plot of log concentration versus percentage of the maximum response (E_{max}) produced by each agonist in individual experiments.

All data are shown as mean ± SEM. Statistical analysis of the data was done with Student's t test at the 5% significance level.

Histamine was used as dihydrochloride (Sigma Chemical Co., St. Louis) and prepared in Jalon solution before being added to the bath. Drug concentrations refer to the free base and are expressed as a final bath concentration in moles per liter.

Results

The spontaneous motility of muscle strips isolated from 82 uteri was studied; 37.5% of all isolated strips showed spontaneous activity during the first hour in the organ bath. The mean ± SEM in minutes required for the uterine strips to start spontaneous motility is summarized in Fig. 1. There was a wide variability among the groups of women studied.

Spontaneous motility of isolated uterine strips from patients with normal menstrual cycles. Spontaneous motility occurred in 35.9% of the muscle strips from uteri without pathologic conditions, 39.6% of the muscle strips from uteri with myomas, and 37.2% of the muscle strips from uteri with adenomyosis. Fig. 2 shows the frequency, force of contraction, and spontaneous uterine activity values obtained in the control group, as well as the myoma and adenomyosis groups. The spontaneous uterine activity in the myoma group was significantly higher than the value obtained in the control group. This latter value was not significantly different from that obtained in the adenomyosis group.

The highest spontaneous uterine activity observed in the myoma group was a result of a marked increase in force of contraction, which was not accompanied by any significant changes in frequency of contractions.

Table I shows the frequency, force of contraction, and spontaneous uterine activity of the control, myoma, and adenomyosis groups in relation to the hormonal phase. It can be seen that the uterine activity developed by the isolated strip from uteri in the secretory phase was similar to the uterine activity developed in the proliferative phase, for each of the three groups.

In addition, in the control group the statistical analysis revealed that the myometrial strips isolated from uteri in the secretory phase developed a spontaneous motility with a significantly lower force of contraction than that of the spontaneous motility of strips isolated from uteri in the proliferative phase. In contrast, the frequency of contraction of myometrium was higher in secretory phase uterus than in proliferative phase uterus. These results were similarly observed in both of two other groups (uteri with myomas and adenomyosis).

Spontaneous motility of isolated uterine strips from preclimacteric patients. The percentages of isolated strips that developed spontaneous motility were 33.3%, 40%, and 50% in preparations from uteri with no abnormalities, myomas, and adenomyosis, respectively.

Fig. 3 shows that the uterine activity of the isolated strips from a uterus with myomas was greater than that observed in preparations isolated from both uteri with adenomyosis and uteri with no pathologic conditions. These differences were a result of a significant increase in force of contraction, which was not accompanied by any significant changes in frequency of contractions.

No significant differences in uterine activity (i.e., frequency and force of contractions) were found among uteri with nonpathologic conditions, uteri with myomas, and uteri with adenomyosis in women with a normal menstrual cycle and uteri that were nonpathologic, had myomas, or adenomyosis in preclimacteric patients.

Spontaneous motility of isolated uterine strips from menopausal patients. The percentages of isolated strips developing spontaneous motility in uteri with no abnormalities, myomas, adenomyosis, and malignant tumor groups were 30.1%, 20%, 31.8%, and 31.3%, respectively.

Fig. 4 shows that the values of uterine activity of the isolated strips from nonpathologic, myoma, and adenomyosis groups were not significantly different, with no modifications in force and frequency of contractions. In contrast, the value of uterine activity was significantly higher in isolated strips of uteri with malignant tumors compared with each of the three groups in menopausal women. This increase in spontaneous uterine motility was mainly a result of an increase in force of contractions.

Both uterine activity and force of contraction values were markedly reduced in isolated strips of uteri with

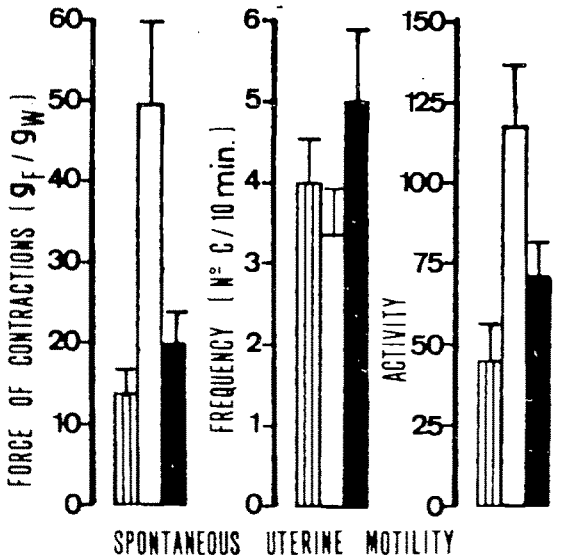


Fig. 2. Frequency (contractions/10 min), force of contraction (g_F/g_W), and spontaneous activity developed by isolated myometrial strips of uteri from women with active sexual cycles and with nonpathologic conditions (▥) (n = 19), myomas (□) (n = 18), and adenomyosis (■) (n = 11). Each value is the mean ± SEM.

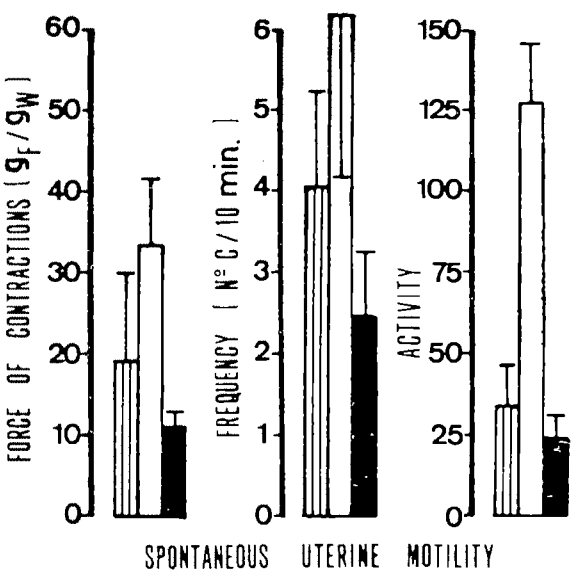


Fig. 3. Frequency (contractions/10 min), force of contraction (g_F/g_W), and spontaneous activity developed by isolated myometrial strips of uteri from preclimacteric women with nonpathologic conditions (▥) (n = 5), myomas (□) (n = 14), and adenomyosis (■) (n = 7). Each value is the mean ± SEM.

myomas compared with those of uteri with myomas of climacteric and women with normal cycles.

In women with nonpathologic uteri, there was a general tendency toward lower uterine activity and force of contractions with decreasing ovarian function. This

Table I. Spontaneous motility of myometrial strips isolated from uteri of women with nonpathologic conditions, myoma, and adenomyosis in proliferative and secretory phases of women with active sexual cycles

	Nonpathologic conditions		*Myomas*		*Adenomyosis*	
	PF (n = 14)	*SC (n = 5)*	*PF (n = 8)*	*SC (n = 10)*	*PF (n = 5)*	*SC (n = 6)*
Uterine activity	48.8 ± 13.6	28.9 ± 11.8	114.6 ± 26.6	120.2 ± 28.4	75.8 ± 16.3	51.6 ± 7.3
Frequency (contractions/10 min)	4.5 ± 0.5	1.9 ± 0.5*	4.8 ± 0.9	2.0 ± 0.5*	7.5 ± 2.2	2.0 ± 0.4*
Force (g_F/g_W)	13.2 ± 3.9	16.4 ± 5.5	31.1 ± 9.4	63.9 ± 14.1*	13.5 ± 3.4	33.5 ± 7.8*

PF, Proliferative; *SC*, secretory. The number of isolated strips used is indicated in parentheses. Values are mean ± SEM.
*$p < 0.05$.

Table II. Effective concentration 50% value and maximal contractile effect for histamine on the myometrial strips isolated from uteri with nonpathologic conditions, myomas, adenomyosis, and malignant tumors of preclimacteric and menopausal women and women with active sexual cycles

	n	EC_{50} *(mol/L)*	E_{max} (g_F/g_W)
Active sexual cycle			
Nonpathologic	16	$6.37 \pm 2.1 \times 10^{-5}$	47.6 ± 6.9
Myoma	13	$2.93 \pm 1.1 \times 10^{-5}$	58.0 ± 7.1
Adenomyosis	8	$9.23 \pm 4.4 \times 10^{-5}$	53.4 ± 18.0
Preclimateric			
Nonpathologic	4	$9.43 \pm 6.2 \times 10^{-6}$	83.0 ± 14.7
Myoma	12	$2.32 \pm 0.7 \times 10^{-5}$	34.6 ± 6.5
Adenomyosis	4	$1.30 \pm 0.7 \times 10^{-5}$	46.1 ± 7.6
Menopausal			
Nonpathologic	17	$2.10 \pm 0.6 \times 10^{-5}$	31.8 ± 6.9
Myoma	10	$4.60 \pm 1.4 \times 10^{-5}$	24.8 ± 9.6
Adenomyosis	6	$3.31 \pm 3.1 \times 10^{-5}$	40.6 ± 6.7
Malignant tumor	6	$6.42 \pm 2.4 \times 10^{-5}$	57.5 ± 13.3

EC_{50}, 50% Effective concentration value; E_{max}, maximal contractile effect; *n*, number of experiments.

tendency was revealed to be significant in the menopausal group.

Effect of histamine. Histamine (10^{-8} to 10^{-3} mol/L) induced concentration-related contractions of the human uterine strips. The force of contraction increased and reached a maximum with 10^{-4} mol/L histamine. The EC_{50} value determined from concentration-response curves was $5.2 \pm 1.0 \times 10^{-5}$ mol/L. The uterine response to histamine varied according to the amount of spontaneous activity shown by the preparation. When the uterine strip exhibited weaker spontaneous activity, this activity declined progressively during a concentration-response curve to histamine. Conversely, when the spontaneous activity developed by the uterine strip was higher, histamine, at the lowest concentrations, produced a superimposed contraction; at higher concentrations, the relaxations between contractions was incomplete, so the force of contractions was increased in a manner similar to that observed when a weaker spontaneous activity is present.

Table II shows that for women with normal menstrual cycles, histamine produced the same maximum degree of contraction and had similar EC_{50} values in each group irrespective of the uterine pathologic condition. In contrast, muscle taken during the secretory phase of the menstrual cycle developed a higher maximal response to histamine than muscle taken during the proliferative phase. However, this difference in responsiveness was not statistically significant (Fig. 5).

The histamine response of myometrial strips from both preclimacteric and menopausal groups was similar to that of the group with normal menstrual cycles. Similarly, the EC_{50} and maximal effect of histamine were unaffected by the pathologic condition of the uterus (Table II).

Comment

The foregoing results confirm previous findings documenting that there was a wide variation in the spon-

taneous contractility of myometrial strips from different uteri.[1-3]

Our results do not support the observation of Lossius and Nesheim[4] who reported that 99% of the muscle strips from nonpregnant uteri showed spontaneous activity. Their study was made with 18 uteri, and the temperature used was 37° C. The greater number and lower temperature used in our study could explain the differences between results. Conversely, our results agree with those of Garrioch,[2] showing that the isolated human myometrium usually begins spontaneous activity within 30 minutes.

It has been reported that uterine spontaneous motility varies according to the phase of the sexual cycle; however, previous reports on differences in spontaneous uterine activity in vitro during the menstrual cycle have been conflicting.[1,2,4,8] Lossius and Nesheim[4] found no modification in the frequency of contraction in relation to hormonal phase. Sandberg et al.[1] found three different types of spontaneous motility in strips from the uterine corpus, although they could not demonstrate any difference between proliferative and secretory phases. However, Garrioch[2] has shown a low amplitude associated with high frequency in the early phase, and that the latter stages are characterized by lower frequency and higher amplitude contractions. Similar observations were found in our study. Moreover, our results are also in agreement with previous in vivo findings.[8]

Our findings in spontaneous activity of the uterus from normal preclimacteric and menopausal women are in accordance with those of Sandberg et al.,[1] who reported a scanty and an intermediate motility in menopausal and preclimacteric groups, respectively. However, the absence of a quantitative study does not permit a more detailed discussion. In addition, similar results have been shown in uterine activity in vivo.[8] Adam et al.[9] have shown marked atrophy in circular and longitudinal uterine layers in preparations taken from ovariectomized guinea pigs. Similar myometrial atrophy during menopause could explain the lower spontaneous uterine activity observed in our study group.

This study explores the possibility that uterine pathologic conditions may mediate changes in spontaneous activity. Our results revealed significant differences between pathologic specimens and normal tissues. In the strips of myomatous uteri, the results show a marked increase in spontaneous uterine activity in both reproductive-aged and preclimacteric women. In contrast, no differences were found when the women were of postmenopausal age. Although in our series no study was done to explain these differences, the occurrence

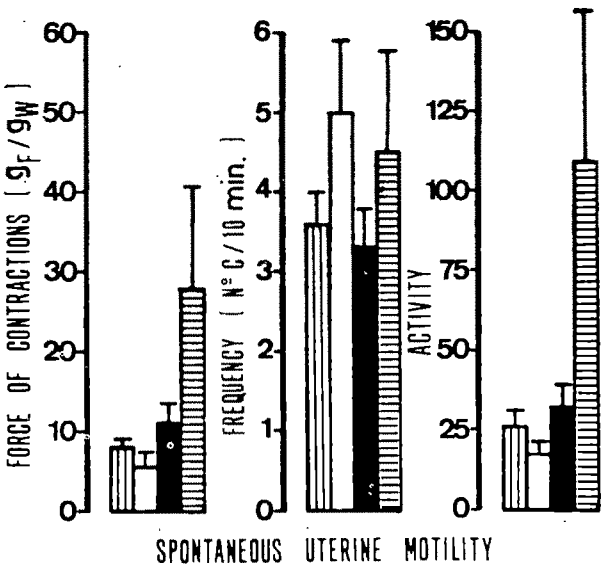


Fig. 4. Frequency (contractions/10 min), force of contraction (g_F/g_W), and spontaneous activity developed by isolated myometrial strips of uteri from menopausal women with nonpathologic conditions (▥) (n = 22), myomas (□) (n = 7), adenomyosis (■) (n = 7), and malignant tumors (▤) (n = 5). Each value is the mean ± SEM.

of increased quantities of steroid receptors in myomas could be related to our results. Soules and McCarty[10] observed normal qualitative cyclic changes in steroid receptors during the menstrual cycle in leiomyomas. Their study agrees with our results, which show two normal cyclic patterns of spontaneous uterine activity in strips taken from uteri with myomas.

Dai et al.[11] suggested that histamine has negligible effects in the human uterus. In contrast, our results show that histamine produces a dose-related contraction of isolated strips of the human uterus and confirm the results described by Farmer and Lehrer.[12] A similar contractile effect of histamine in guinea pig uterus has been reported. Our results also show that the contractile effect of histamine is quantitatively the same, whether the specimen is obtained during either of the two stages of the menstrual cycle or after the menopause. A decrease during aging in sensitivity to histamine has been reported in guinea pig trachea, but as in our results, this change in the contractile effect of histamine is absent in bronchial and parenchymal preparations.[13] In contrast, Eltze[14] failed to find changes in the inhibitory response to histamine on the isolated rat uterus during the menstrual cycle. Similarly, in our study no significant differences in the uterine contractile effect of histamine are shown in the proliferative or secretory phases.

It is well documented that in some airway diseases

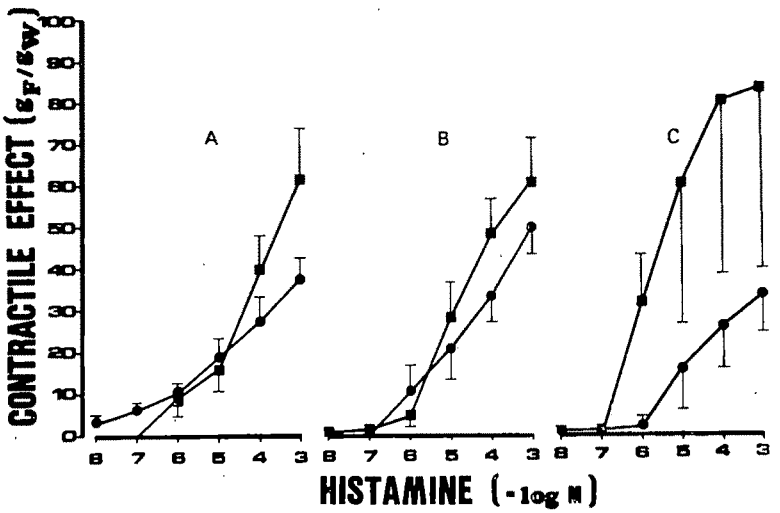


Fig. 5. Dose-response curves to histamine on isolated myometrial strips taken from uteri of women with nonpathologic conditions (**A**), myomas (**B**), and adenomyosis (**C**) of women with active sexual cycles, in proliferative (●) and secretory (■) phases. Each point shows the mean from at least four experiments, and the SEM is shown.

there is hyperreactivity to histamine, and it has been suggested that the existence of hypertrophy and hyperplasia of airway smooth muscle may account for the heightened reactivity to contractile agonists. In this sense, the myometrial strips used in this study were obtained from uteri with pathologic conditions that produce quantitative and qualitative modifications of the smooth muscle mass. Hence, it seems likely that the contractile response to histamine could be modified according to the pathologic conditions. Our results failed to demonstrate a significant modification of EC_{50} and E_{max} of histamine when the dose-response curves of histamine were performed on isolated myometrial strips obtained from different pathologic groups of uteri. The fact that the strips used in our study were taken from macroscopically normal areas of the uterus could explain the lack of modifications in the dose-response curves of histamine found. Pathogenic mechanisms other than those proposed in airway abnormality must occur in uterine pathology and also could explain the different results obtained with histamine in these two tissues.

In summary, the results of this study provide evidence that the spontaneous motility of the isolated strips of human corpus uteri varies according to the uterine pathologic condition and also varies in relationship with menopause. They also confirm the existence of two different sexual phase–related patterns in spontaneous motility of the isolated myometrial strip of human uteri. In addition, it was not possible to demonstrate a significant change in the uterine response to histamine with the uterine abnormality studied.

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A new tocolytic agent: Development of an oxytocin antagonist for inhibiting uterine contractions

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Chicago, Illinois

A potent oxytocin antagonist has been developed and tested on both the rat and human uterus. In the rat the oxytocin antagonist: (1) inhibited in vitro and in vivo uterine contractions in the nonpregnant animal in response to exogenous oxytocin, (2) inhibited milk letdown, and (3) disrupted the progress of labor. In addition, the oxytocin antagonist inhibited the in vitro contractile response to exogenous oxytocin of human myometrial tissue obtained by cesarean section at term. The results of these studies suggest that the oxytocin antagonist can be used to study the role of oxytocin in labor and has the potential of inhibiting preterm labor in humans. (AM J OBSTET GYNECOL 1990;163:195-202.)

Key words: Oxytocin antagonist, uterine contractions, tocolytic, preterm labor

The contribution of maternal and fetal oxytocin to the initiation and progress of labor is poorly understood. The studies in the literature are conflicting and enigmatic. There are reports that oxytocin levels in the peripheral plasma in humans increase with gestational age or remain unchanged,[1,2] increase at different stages of labor, or show no alterations.[3,4] Similar ambiguities also exist with studies in other species. There are indications the fetus might be an important contributor of oxytocin to labor,[3,5] but other studies refute these data.[6] Also, there are reports that imply that maternal oxytocin does not play a role in parturition in rats[7,8] or humans.[9]

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Additional studies have shown that oxytocin receptor levels increase dramatically in uterine tissue just before and at the time of labor in several species, including rats and humans.[10,11] This is interpreted to mean that enhanced secretion of oxytocin is not required and that constant levels of oxytocin in the face of augmented uterine sensitivity to oxytocin would result in incremental changes in uterine activity that culminate in labor.

Recent reports have focused on the development of an oxytocin antagonist for inhibiting uterine contractions.[12-15] The purpose of the present study was to develop a potent oxytocin antagonist to be used to study the role of oxytocin in pregnancy and labor and for the potential clinical use of inhibiting preterm labor in humans. The results of this study show that a potent oxytocin antagonist has been developed; oxytocin appears to be important in the labor process in rats, and the oxytocin antagonist inhibits the response of human myometrial tissue to exogenous oxytocin in vitro. These data suggest that the oxytocin antagonist has the potential of inhibiting preterm labor in humans.

Material and methods

Animals. Virgin (200 to 220 gm) and timed-pregnant (320 to 400 gm) Sprague-Dawley–derived Holtzman rats (Madison, Wis.) were used in these studies. The rats were housed in rooms with controlled light cycles (14 hours light and 10 hours dark) with lights on at 6 AM and given water and food as desired. The protocols in this report have been approved by the Animal Care Committee at the University of Illinois.

Synthesis of oxytocin antagonists. Three oxytocin analogs were synthesized with the solid phase method as previously reported[16]: (1) [β-mercapto-β, β-cyclopentamethylene propionic acid[1], D-Trp[2], Ile[4], Arg[8]]-vasopressin, which will be referred to as oxytocin antagonist 1; (2) its 2-aminodane, 2-carboxylic acid[2] analog; and (3) a D-Phe[2]-oxytocin antagonist analog. Analog 3 was previously reported.[17]

Oxytocin bioassays. Uterine horns from rats in natural estrus were used for the bioassays according to the methods of Holton[18] as modified by Munsick.[19] The tissue was placed longitudinally in a 10 ml organ bath containing van Dyke–Hastings solution with 0.5 mmol/L ionized magnesium at 37° C and gassed with 95% oxygen and 5% carbon dioxide. Ionized magnesium was included in the media since oxytocin antagonistic activity in vitro has been reported to correlate better with in vivo results when it is present.[20] The resting tension on the tissue was 1 gm, and isometric contractions were recorded with a force-displacement transducer FTO3 (Grass Instruments, Quincy, Mass.) and a model 79 polygraph (Grass Instruments). Contractile response of uterine tissue exposed to oxytocin (Bachem, Inc., Torrance, Calif.) for 3 minutes was determined by integrating the area under the curve with a model 7P10 integrator (Grass Instruments). The inhibitory activity (pA_2) of the oxytocin antagonist was determined by the method of Schild.[21] After a cumulative dose-response curve was initially performed with oxytocin, a concentration of oxytocin equal to 90% of the maximum response was used for the antagonist studies. The uterine tissue was exposed to the oxytocin antagonist for 5 minutes before the oxytocin was added; the latter response was then recorded for 1 minute. Four-point assays at three different doses of oxytocin antagonist were performed. The pA_2 estimates were from the average of four or more assays. The pA_2 is defined as the negative logarithm of the molar concentration of an antagonist that reduces the response to the agonist by one-half.[21] Thus the higher the pA_2 value, the more potent the antagonist.

Antidiuretic hormone bioassays. Anti–antidiuretic hormone activity was determined by the method of Jeffers et al.,[22] as modified by Sawyer.[23] Rats were initially gavaged with a volume of 12% ethanol in 0.05% saline solution equal to 5% of body weight. Subsequently the animals were kept hydrated to 8% above initial body weight with 2% ethanol in 0.05% saline solution. The jugular vein was cannulated (PE-50 tubing; Clay Adams, Parsippany, N.J.) for injection of materials and the bladder was catheterized with PE-90 tubing via an abdominal incision for monitoring urine output. Urine drops were counted with a photoelectric pulse sensor transducer (model PPS, Grass Instruments). Body temperature, determined rectally, was maintained at 37° C throughout the experiment with a heat lamp. The end point for the bioassay was urine flow rate. Antidiuretic hormone (Bachem, Inc.) reduces the flow rate and an antagonist diminishes this response. An antidiuretic hormone concentration equivalent to approximately 90% of the maximum response was used as the standard. Ten minutes after the oxytocin antagonist was injected (20 minutes if agonist activity was present), the antidiuretic hormone standard was administered and the response was recorded over a 10-minute period. Concentrations of oxytocin antagonist that altered the response >50% and <50% of the response to antidiuretic hormone alone were used. Three-point assays were performed. The next oxytocin antagonist dose was not administered until the response to antidiuretic hormone was within 10% of the original value. This often took between 30 and 60 minutes. The pA_2 values calculated with this method are substantially lower than if a set time of 30 minutes is allowed between the last antidiuretic hormone injection to the next oxytocin antagonist administration as described by Sawyer et al.[20] The pA_2 is then calculated by the method of Schild.[21] This bioassay was repeated on at least four different animals to obtain a mean pA_2 value for a given antagonist.

In vivo oxytocic assays. Response of the estrous rat uterus in vivo to oxytocin and oxytocin antagonist was tested as described by Bisset et al.[24] and Sawyer et al.[20] with modification. Rats were anesthetized with chloral hydrate (500 mg/kg) intraperitoneally, and a balloon-tipped, water-filled polyethylene catheter (PE-50) was introduced through a small incision at the ovarian end of the uterus and tied in place. Intrauterine pressure was recorded with a Gould P23 ID pressure transducer and a polygraph (Grass Instruments). A PE-50 polyethylene cannula was placed in the jugular vein for infusing oxytocin, oxytocin antagonist 1, or prostaglandin E_2 or $F_{2\alpha}$. One hundred nanomoles of oxytocin and oxytocin antagonist 1 or 300 nmol of prostaglandins was administered as a bolus injection.

Milk letdown studies. Three to four days after delivery rats were anesthetized with chloral hydrate (500 mg/kg) and a PE-50 polyethylene cannula was placed in the carotid artery for infusing heparin–saline solution or oxytocin analogs. The cannula was led to the dorsal surface and exited the skin between the scapula.

Table I. Antioxytocic and antidiuretic potencies of oxytocin analogs

	pA_2 estimates			
	Antioxytocic activity		*Antidiuretic hormone activity*	
Analog No.	*n*		*n*	
1	22	7.62 ± 0.02	8	7.40 ± 0.07
2	2	0	—	—
3	10	7.35 ± 0.01	8	7.66 ± 0.05

See text for description of compound structures (mean ± SEM).

The mothers were fitted with jacket (Alice King Chatham, Los Angeles) and tether, the latter through which the cannula was led outside the cage. The oxytocin analogs were infused at a rate of140 ng/min with a Harvard infusion pump (Harvard Apparatus, South Natick, Mass.). The newborns were reduced to 7 pups per mother at the beginning of the study. Newborn weight gains and the presence of milk in the stomach were monitored as indications of milk letdown. The presence of milk in the stomach is easily observed since the abdominal wall is transparent during the first 15 days of life.

Inhibition of labor. Rats were operated on during day 19 of pregnancy, cannulas were placed in the jugular vein, and a jacket with a tether was placed on the rat as described above for the milk letdown studies. Peptides or control infusions were begun at 9 AM on day 21 of pregnancy and continued until delivery. Peptides were infused at a rate of 140 ng/min.

In vitro oxytocic assays on human myometrium. A full-thickness piece of uterine tissue was obtained from the upper edge of an incision site of a low transverse section at the time of elective cesarean section from eight women at term pregnancy (38 ± 0.5 weeks). A section of transverse myometrial tissue of approximately 1 × 0.2 × 0.2 cm weighing approximately 50 mg was removed and placed in an organ bath, and uterine contractions were monitored as described above for the rat in vitro oxytocic bioassays. Because of the variation in the time of day the samples were obtained and the variation in baseline activity, dose-response curves and pA_2 estimations were not performed in these initial studies. The observation recorded was whether a given amount of oxytocin antagonist 1 could inhibit the response to a given amount of oxytocin and the degree of this inhibition. Responses were determined by integrating the area under the contractile curve for 15 minutes, subtracting the baseline value, and then dividing the results by the tissue weight to give integrated units per milligram of tissue. Informed consent was obtained from all subjects. The study protocol was approved by the University of Illinois Institution Review Board.

Statistical methods. Data in Table II were analyzed by analysis of variance, and, when significant, differences were detected by Duncan's multiple range test.[25] Data in Fig. 5 were analyzed by paired *t* test.[25]

Results

Oxytocin and antidiuretic hormone bioassays. Table I shows the results of the oxytocin bioassay. Of the compounds tested oxytocin antagonist 1 had the highest pA_2 value (7.62). This oxytocin antagonist showed no agonist activity at the highest level tested (10 μmol/L). Note that analog 2 had no antioxytocin activity and thus was only tested in two bioassays. Two assays is a small number, but one must remember that these are four-point assays tested at three different doses; thus each assay was screened for activity 12 times. Oxytocin antagonist activity was not detected in any of these tests.

In the antidiuretic hormone bioassay the estimated pA_2 for oxytocin antagonist 1 was 7.40. No antidiuretic hormone–like agonist activity was detected at the maximum doses tested. Since oxytocin antagonist 1 showed the highest pA_2 in the antioxytocin assay and the lowest pA_2 in the anti–antidiuretic hormone assay on comparison with analogs 2 and 3, it was chosen for further study.

In vivo oxytocic assays. Fig. 1 shows a representative response of in vivo uterine contractions of an estrous rat in response to oxytocin (100 nmol) in the presence and absence of oxytocin antagonist 1. A bolus injection of oxytocin antagonist (100 nmol) blocked the stimulatory activity of oxytocin but not that of prostaglandin F_{2a} or prostaglandin E_2 (300 nmol each). The latter results suggests that oxytocin antagonist 1 has a specific effect on the uterus and not a general, nonspecific tocolytic effect. Also note that about 1 hour after the last injection of oxytocin antagonist 1 the uterus still did not respond to oxytocin but did respond to prostaglandin E_2.

Milk letdown studies. Figs. 2 to 4 illustrates representative results of the milk letdown experiments. Fig. 2 depicts a control animal that received a heparin–saline solution infusion only. The newborn growth rate was constant, and milk was always found in the newborns' stomachs on every observed day. Fig. 3 shows

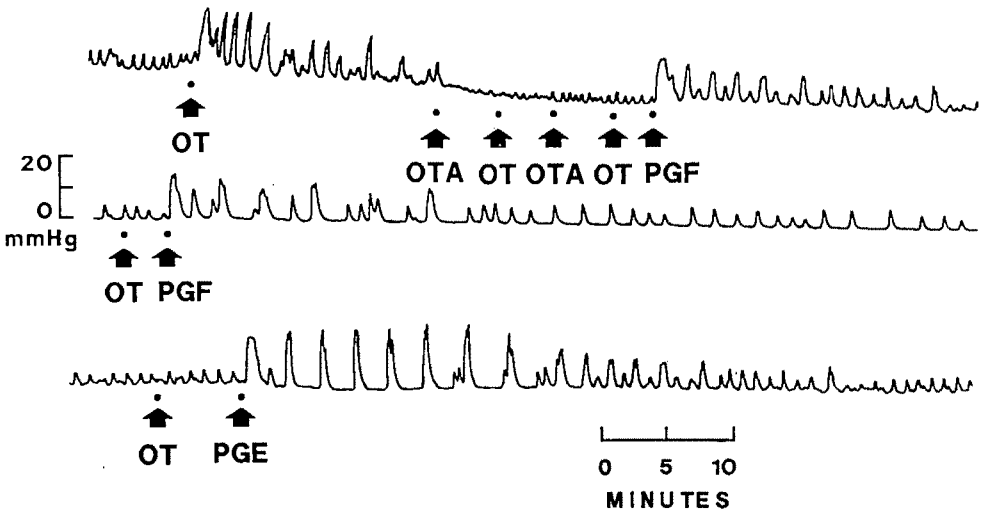


Fig. 1. The in vivo contractile response of an estrous rat uterus to a 100 nmol intravenous bolus injection of oxytocin *(OT)* and the ability of a 100 nmol intravenous bolus injection of the oxytocin antagonist *(OTA)* to block the response to *oxytocin* but not to prostaglandin F or E (300 nmol intravenous bolus, respectively).

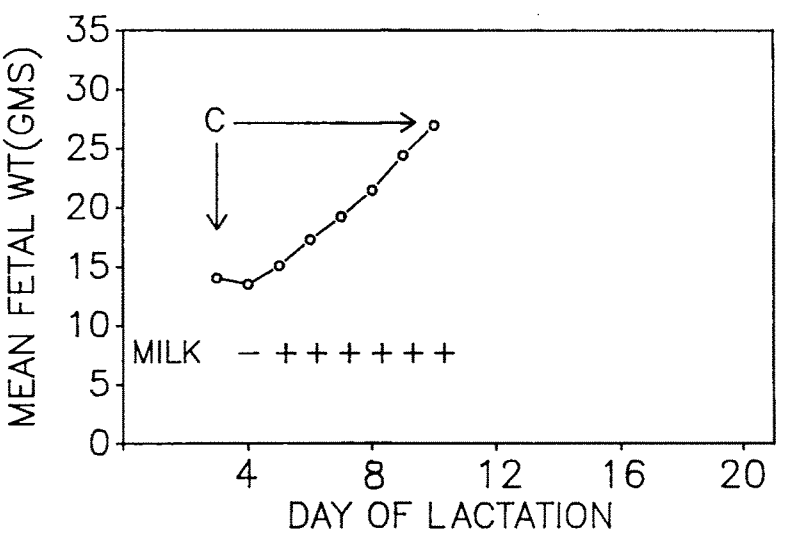


Fig. 2. Relationship of mean weight and the presence (+) or absence (−) of milk in the stomachs of newborn rats to the day of lactation in a mother cannulated on day 3 of lactation and infused with heparin–saline solution *(C)* until day 10.

the effects of oxytocin antagonist 1 on milk letdown. Within 24 hours after oxytocin antagonist 1 was given, the neonatal growth rate was diminished and milk was absent from the newborns' stomachs. Twenty-four hours after oxytocin antagonist 1 infusion was stopped, milk was present in the stomach and growth was renewed. Fig. 4 illustrates the results of infusing analog 2, an oxytocin analog that was found to have no inhibitory activity in the oxytocic bioassay. Neither growth of the newborn nor presence of milk in the stomach was inhibited. These results suggest that the effect observed with oxytocin antagonist 1 on milk letdown was not simply a nonspecific effect, such as a sympathetic discharge that might prevent milk letdown.

It was found in studies not shown that milk letdown began within 6 hours after the infusion of oxytocin antagonist 1 was stopped. This was tested by placing fasted newborns into the cages of mothers every hour after oxytocin antagonist 1 infusion was stopped and observing once every hour the newborns' stomachs for the presence of milk.

Labor inhibition studies. As shown in Table II oxytocin antagonist 1 delayed ($p < 0.05$) the initiation of labor on comparison with the controls that were op-

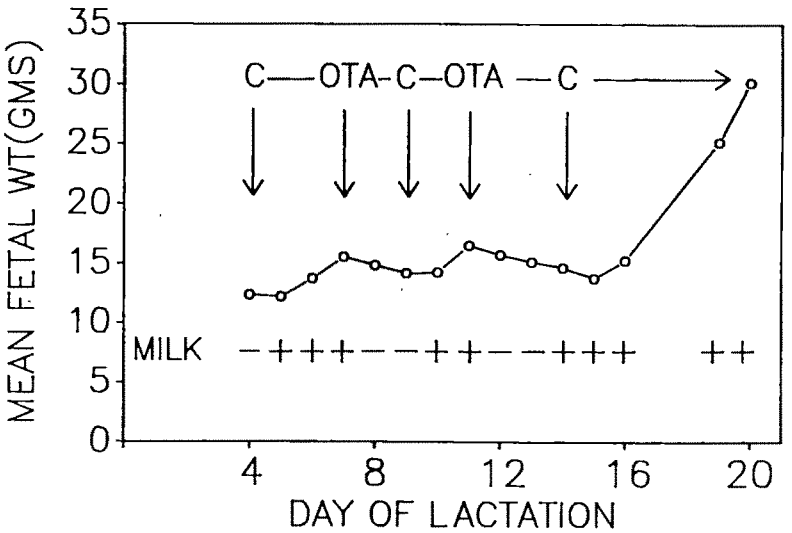


Fig. 3. Similar to Fig. 2, except the oxytocin antagonist was infused at 140 nmol/min on the days indicated. Note the exquisite control of milk letdown via use of the oxytocin antagonist.

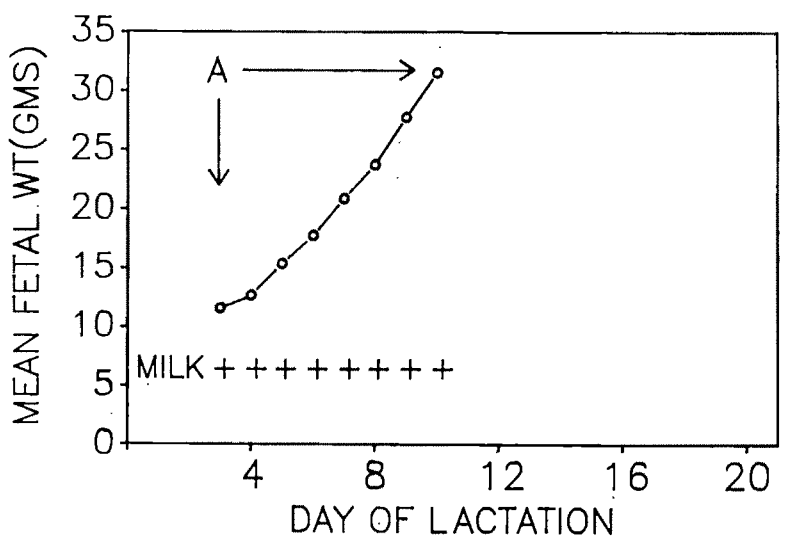


Fig. 4. Similar to Fig. 3, except an inactive oxytocin analog, analog 2 *(A)*, was infused at 140 nmol/min. No inhibition of milk letdown was detected, suggesting the results in Fig. 3 were not due to a nonspecific effect such as a sympathetic discharge.

erated on (40.0 vs 25.9 hours, respectively). However, the most obvious effect was on the length of delivery from the first to the last fetus, which was prolonged ($p < 0.05$) from 8.3 to 16.5 minutes per fetus. The oxytocin antagonist 1–treated group had many fetal deaths that were probably related to hypocontractility. Toxicology studies will have to be performed so that we can accurately assess the potential effects of the oxytocin antagonist on the fetus.

In vitro oxytocic assays on human myometrium. The addition of oxytocin antagonist 1 to the tissue bath containing human myometrial tissue 5 minutes preceding oxytocin administration significantly ($p < 0.05$) diminished the response to oxytocin (Fig. 5). Thus oxytocin antagonist 1 was capable of blocking the response to oxytocin in human tissue, similar to the response by rat uterine tissue in vitro. This suggests that oxytocin antagonist 1 has the potential of inhibiting spontaneous in vivo uterine contractions in humans and possibly preterm labor contractions, if such activity is controlled by oxytocin.

Comment

The development of a potent and specific oxytocin antagonist will be useful for studying the contribution of endogenous oxytocin to uterine contractile activity

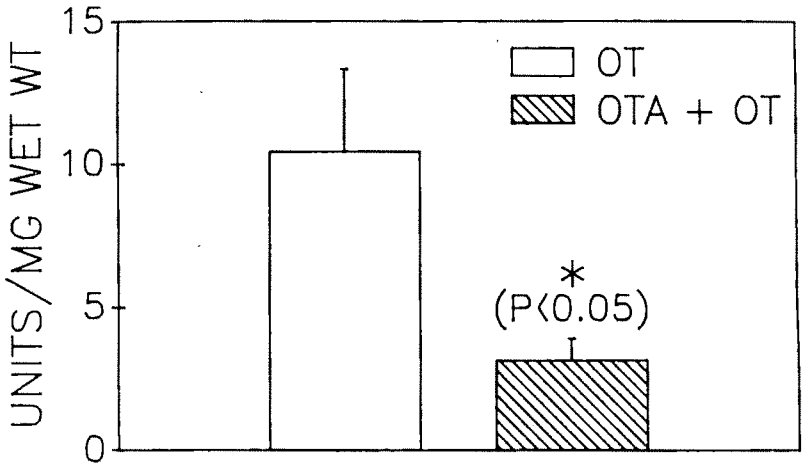


Fig. 5. The in vitro integrated contractile response of human myometrial tissue obtained at cesarean section to 55 nmol/L oxytocin and its inhibition by 35 nmol/L of oxytocin antagonist. The mean inhibition was 67% (N = 8, ±SEM).

Table II. Effect of the oxytocin antagonist on delivery time and progress of labor in the rat

	n	*Initiation of delivery (hours) beginning on day 21*	*No. of fetuses*	*Delivery time per fetus (min)*	*Fetuses*	
					Alive	*Dead*
Controls	11	18.6 ± 3.1[a]	12.8 ± 0.8[a]	6.4 ± 0.4[a]	13.0 ± 0.7[a]	0.1 ± 0.1[a]
Controls operated on	8	25.9 ± 4.2[a]	11.4 ± 0.7[a]	8.3 ± 1.0[b]	11.0 ± 0.9[a,b]	0.4 ± 0.3[a]
Oxytocin antagonist treated, operated on	9	40.0 ± 5.3[b]	12.3 ± 0.8[a]	16.5 ± 1.8[c]	7.8 ± 2.0[b]	4.2 ± 1.3[b]

Data with different superscripts are significantly different ($p < 0.05$) from each other (mean ± SEM).

throughout pregnancy and at the time of labor. In addition, it has potentially significant clinical application as a tocolytic for preterm labor. This study reports the development of a potent oxytocin antagonist that has been shown to inhibit in vitro uterine contractions of the estrous rat uterus in response to exogenous oxytocin with an estimated pA_2 of 7.62. The pA_2 estimation would be greater if ionized magnesium had been absent from the bioassay buffer. However, ionized magnesium was added since it has been reported to give better correlations with in vivo activity.[20] In addition, the pA_2 would be enhanced if amplitude of the first contraction rather than integrated area under the curve was used as the end point of the bioassay (e.g., amplitude vs integration: oxytocin antagonist pA_2, 8.4 vs 7.62, respectively). The pA_2 estimate from the antidiuretic hormone bioassay was 7.40; thus the oxytocin antagonist has the potential of inducing diuresis in vivo. There were indications of anti–antidiuretic hormone activity (i.e., increased water uptake) in some, but not all, pregnant rats receiving the oxytocin antagonist.

In addition to inhibiting in vitro uterine contractions, this study also demonstrates that oxytocin antagonist 1 can inhibit in vivo uterine contractions in the rat induced by exogenous oxytocin. It was intriguing to find that the inhibitory effect of an intravenous bolus injection of 100 nmol of oxytocin antagonist 1 lasted for more than 1 hour compared with oxytocin whose effect lasted approximately 15 minutes when given at equivalent doses. This suggests oxytocin antagonist 1 may have a fairly long half-life in vivo, as compared with oxytocin. Since the response to oxytocin antagonist 1 in vitro can be washed away within 15 minutes, this indicates that the effectiveness of the oxytocin antagonist in vivo may not be only via its competition for the oxytocin receptor but via an increased half-life as well. Thus the estimated effectiveness of oxytocin antagonist 1 may actually be greater than anticipated from the pA_2 estimation of 7.62 determined from in vitro oxytocic bioassays, which mainly reflect the interaction of oxytocin antagonist 1 with the oxytocin receptor.

The one unequivocal function for oxytocin is its role in milk letdown. The present study has shown that this process in lactating mothers can be exquisitely controlled by oxytocin antagonist 1. Furthermore, it was shown that the effect of oxytocin antagonist 1 was most likely not via a nonspecific response, such as a sym-

pathetic discharge that would inhibit milk letdown, since an inactive oxytocin analogue (analog 2) had no effect on milk letdown. Besides inhibition of milk letdown, oxytocin antagonist 1 may be interfering with prolactin release and thus lactogenesis. Oxytocin has been implicated in prolactin release.[26] However, since it only took 6 hours after oxytocin antagonist 1 infusion was stopped for milk to be detected in the newborn's stomach, this effect, if any, is not profound or long-term. This is an important observation since women taking an oxytocin antagonist to prevent preterm labor may want to nurse their child soon after delivery. This study in rats, as well as in pregnant baboons (unpublished observations), indicates this should not be a problem.

When given to pregnant rats about to deliver, oxytocin antagonist 1 appeared to delay labor, but more apparent was that it prolonged the progress of labor. This suggests that endogenous oxytocin may be more important in the progress and not the initiation of labor in the rat. Because of the limited supply of oxytocin antagonist 1 a dose-response study was not performed in vivo in these initial studies. Perhaps at higher doses the actual initiation of labor can be delayed. Further studies will be needed to determine this possibility.

The observation that about half the newborns were dead at delivery was not surprising considering the prolonged labor that occurred. It is unlikely that oxytocin antagonist 1 is contributing directly to the fetal deaths. However, this will only be resolved by toxicology studies directed toward this specific question.

Finally, in initial attempts to determine if oxytocin antagonist 1 will be effective in humans, in vitro studies on eight separate myometrial tissues showed that oxytocin antagonist 1 could inhibit the myometrial contractile response to exogenous oxytocin. This, along with recently reported studies by Akerlund et al.,[12] that preterm labor contractions in humans could be inhibited with an oxytocin antagonist, suggests that oxytocin antagonist 1 has the potential of inhibiting preterm labor in women.

The importance of an oxytocin antagonist as a tocolytic is its greater specificity (thus with fewer side effects) in comparison with current modalities of treating preterm labor such as sympathometics, magnesium sulfate, and calcium blockers. However, recent reports of finding oxytocin in tissue other than the hypothalamus and pituitary require reassessment of the potential side effects of the oxytocin antagonist.

In summary, this study has reported the development of a potent oxytocin antagonist (1) that inhibited in vitro and in vivo uterine contractions of the nonpregnant rat uterus in response to exogenous oxytocin; (2) that inhibited milk letdown in the lactating rat, (3) that disrupted the progress of labor in the rat, and (4) that inhibited the in vitro myometrial response to exogenous oxytocin in tissue obtained from women via cesarean section at term.

In conclusion, a potent oxytocin antagonist has been developed that can be used to study the role of oxytocin in uterine contractile activity throughout pregnancy and has the potential for inhibiting preterm labor contractions in humans.

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Differential sensitivities of fetal muscle groups to *d*-tubocurarine

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Nine fetal lambs were instrumented for long-term intrauterine recording of electrocorticogram electrooculogram, electyromyogram of the dorsal neck muscle, the quadriceps femoris, and the diaphragm, monitoring of blood pressure, and measurement of heart rate. *d*-Tubocurarine (0.1 to 0.8 mg) was administered intravenously to the fetus over a 1-minute interval. Increasing doses of *d*-tubocurarine selectively blocked various muscle groups, with the extraocular muscles being the most sensitive. Comparison of the median effective dose for neuromuscular blockade of the extraocular muscles/nuchal muscle/diaphragm was 1:2.5:6. The duration of action of *d*-tubocurarine was directly related to the relative sensitivities of the different muscle groups, which are ranked from most sensitive to least sensitive as extraocular muscles, nuchal muscle, and diaphragm. Fetal electrocorticogram continued to cycle despite total neuromuscular blockade. However, there was an increase in synchronized and mixed activity, which was predominantly due to an increase in cycle numbers, and a decrease in desynchronized activity, which was predominantly due to shorter cycle lengths. During total neuromuscular blockade, there was also a significant decrease in heart rate during synchronized and mixed electrocorticogram states but not during a desynchronized electrocorticogram state, thus resulting in a loss of the heart rate difference normally seen between synchronized and desynchronized states. Fetal blood pressure did not change with total neuromuscular blockade. (AM J OBSTET GYNECOL 1990;163:202-9.)

Key words: *d*-Tubocurarine, pancuronium, neuromuscular blockade, fetal paralysis

Neuromuscular blockers are increasingly being used to prevent fetal movements during a variety of intrauterine fetal therapy such as ultrasonography-guided intraperitoneal or intravascular transfusions or shunt placement.[1-4] Fetal movement makes these procedures more difficult and may increase the risk of injury to the fetus. Direct intramuscular or intravenous administration of either *d*-tubocurarine or pancuronium to the fetus was found to be effective in producing complete fetal paralysis as determined by maternal perception[4] or ultrasonographic monitoring.[3] Both *d*-tubocurarine and pancuronium were found to have a rapid onset of action, and the duration of action was

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found to be a function of the dose used. Limited experience to date suggests that fetal neuromuscular blockade is an invaluable adjunct to invasive intrauterine procedures, and the short-term use of neuromuscular blockers appears to be without significant adverse effects.

It has been suggested in a previous study that one concern with total neuromuscular blockade in the fetus is the potential need for emergency delivery because of fetal distress during the procedure.[3] Ultrasonographic monitoring revealed that fetal paralysis may last several hours depending on the drug and the dose given.[3] However, these investigators only reported on fetal movements and did not specifically monitor fetal diaphragmatic movements. Differential sensitivities of muscle groups to nondepolarizing neuromuscular blockers have been reported since the late 1940s.[5] The relative sensitivities of the nonrespiratory muscles in general and the respiratory muscles reflect the therapeutic index or safety margin of the drug. Studies in adults demonstrated that the sensitivity of nonrespiratory muscles was at least twice that of the diaphragm, and the diaphragm recovered twice as rapidly as the other muscles.[6,7] The relative sensitivity of various fetal muscles to nondepolarizing neuromuscular blockers is not known.

The objective of the present study was to describe the dose-response and time-action characteristics of *d*-tubocurarine on different muscle groups in the fetal lamb. In addition, we examined the effects of *d*-tubocurarine on fetal cardiovascular function and electrocortical activity. Chestnut et al.[8] recently reported that intravenous administration of *d*-tubocurarine to the fetal lamb significantly decreased fetal heart rate and arterial pressure while pancuronium significantly increased fetal heart rate and arterial pressure. However, the extent of neuromuscular blockade achieved with the single dose of neuromuscular blocker used was not known. We report here on the effects of varying degrees of neuromuscular blockade on fetal cardiovascular function and electrocortical activity.

Methods

Animal preparation. Nine fetal lambs ranging from 124 to 140 days of gestation were used in this study, in accordance with guidelines approved by the institution for the care and use of animals. Operation was conducted 5 to 29 days before the drug study. Details of the surgical procedure have been published previously.[9] Briefly, polyvinyl catheters were placed in the descending aorta for monitoring of fetal blood pressure and heart rate and in the inferior vena cava for administration of *d*-tubocurarine. Stainless steel electrodes were implanted in the dorsal neck muscle, the quadriceps femoris and the diaphragm for electromyogram recording. Eye movements (electrooculogram) were monitored with a pair of stainless steel screws implanted over the superior orbital ridge, and electrocortical activity (electrocorticogram) was monitored with stainless screws over the parietal cortex.

Study protocol. On the day of the study, the sheep was placed in an experimental cart and simultaneous recording of fetal blood pressure, fetal heart rate, and nuchal and quadriceps electromyogram, diaphragmatic electromyogram, electrooculogram, and electrocorticogram were obtained for a 3-hour control period on a Gould analog recorder with appropriate amplifiers and band-pass filters (electromyogram, 100 to 1000 Hz; electrooculogram, 1 to 10 Hz; electrocorticogram, 1 to 30 Hz). *d*-Tubocurarine was administered intravenously to the fetus over a 1-minute period. A total of four doses was studied (0.1 to 0.8 mg), and the order of dose administration was randomized. Each animal received only one dose of *d*-tubocurarine on any given day and at least 2 days was allowed between studies. Simultaneous recording of all fetal parameters continued until recovery from neuromuscular blockade.

Data analysis. The extent of neuromuscular blockade for each muscle was determined after *d*-tubocurarine administration and represented as a percent of control, with each animal serving as its own control. A log dose-response curve was then constructed for each muscle. From the best-fitting curve, the median effective dose was determined for each of the three muscles. The duration of action of *d*-tubocurarine on the three different muscles was compared by means of both quantal and graded time-action plots. The quantal time-action curve was plotted as the percent of animals with 100% blockade of each of the three muscles as a function of time after *d*-tubocurarine administration. The graded time-action curve was plotted as the percent of control electromyogram amplitude for the three different muscles as a function of time after drug administration.

The electrocorticogram was scored as three distinct states: desynchronized (low-voltage fast activity), synchronized (high-voltage slow activity), and mixed (intermediate voltage activity). The incidence of each of the electrocorticogram states was determined after *d*-tubocurarine administration and compared with predrug control values. The number of cycles of each state per hour and the mean duration of each state also were compared with control values.

Mean fetal blood pressure and fetal heart rate were determined for each electrocorticogram state in the control period and after *d*-tubocurarine administration. Statistical differences were ascertained by two-way analysis of variance with subsequent post hoc tests (Systat statistical software, Evanston, Ill.).

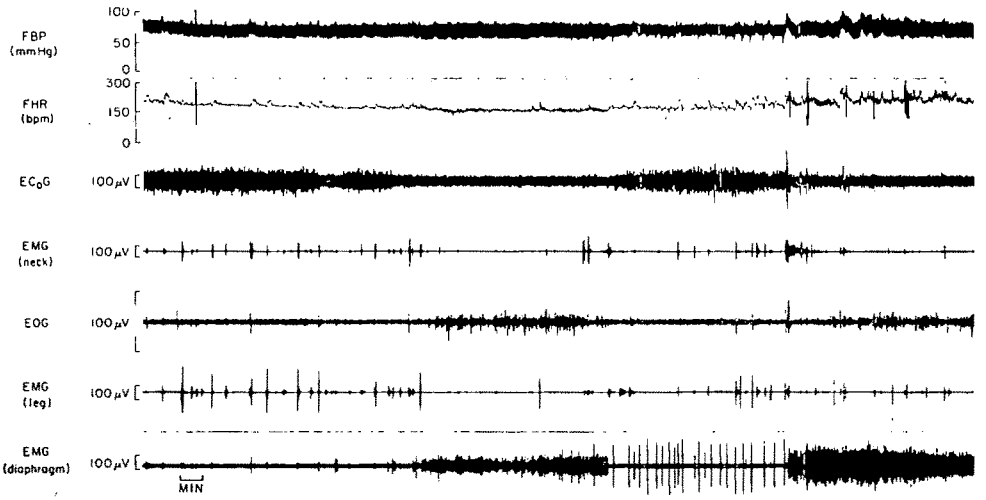


Fig. 1. A representative polygraphic recording obtained from fetal lamb before *d*-tubocurarine administration. Note cyclic activity in different muscle groups associated with different electrocorticogram patterns. *FBP*, Fetal blood pressure; *FHR*, fetal heart rate; *ECoG*, electrocorticogram; *EMG (neck)*, electromyogram of nuchal muscle; *EOG*, electrooculogram; *EMG (leg)*, electromyogram of hind limb muscle; *EMG (diaphragm)*, electromyogram of diaphragm.

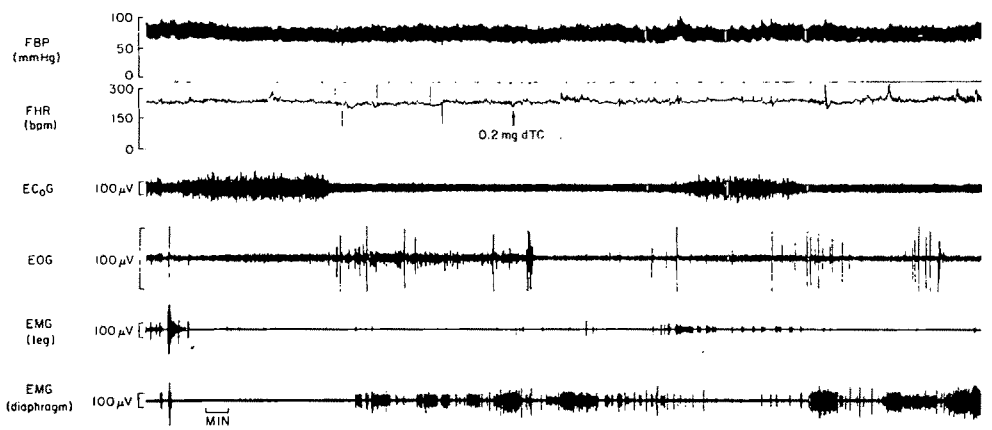


Fig. 2. Polygraphic recording showing effects of 0.2 mg of *d*-tubocurarine administered intravenously over 1 minute to fetal lamb. Note abrupt cessation of all eye movements and a decrease in amplitude of nuchal electromyogram bursts. Diaphragmatic activity was not affected. For explanation of abbreviations see legend to Fig. 1.

Results

Nineteen experiments were performed in nine chronically instrumented animals, with three to six animals studied at each dose level of *d*-tubocurarine.

Fig. 1 shows a representative polygraphic recording obtained during the control period. The electrocorticogram can be seen to alternate between synchronized and desynchronized patterns, with an occasional brief period of a mixed pattern in which there are slower waves of intermediate amplitude. The desynchronized periods are associated with a lower heart rate, rapid eye movements, and breathing movements. On the other hand, the synchronized periods are associated with a higher heart rate, an occasional burst of electromyogram activity in the diaphragm, both tonic and phasic activity in the nuchal and hind limb muscles, and an absence of eye movements.

Administration of 0.2 mg of *d*-tubocurarine to the fetal lamb resulted in an abrupt cessation of all eye movements during a desynchronized electrocorticogram (see Fig. 2). There was also a decrease in the amplitude of the electromyogram bursts in the nuchal muscle during the synchronized electrocorticogram period. Fetal breathing movements were not affected by this dose of *d*-tubocurarine, and cyclic activity in the electrocorticogram was unchanged.

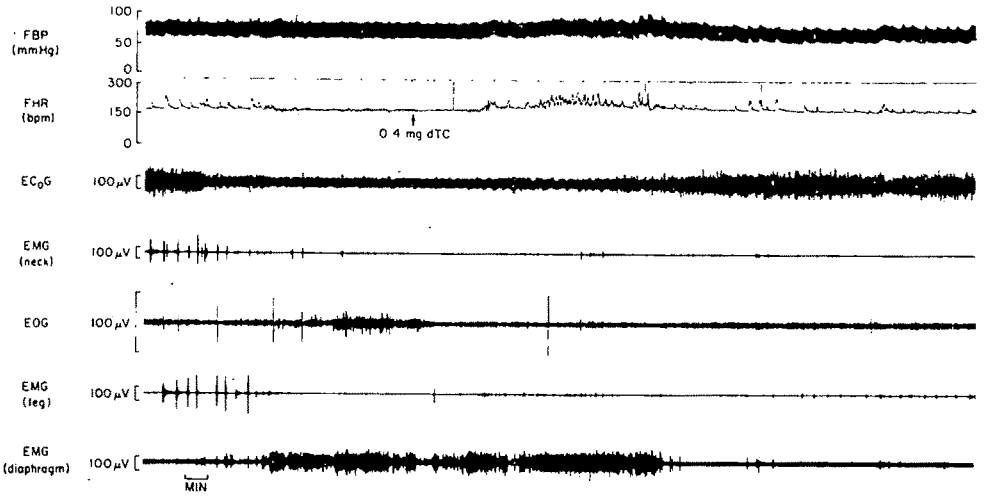


Fig. 3. Polygraphic recording showing effects of 0.4 mg of *d*-tubocurarine administered intravenously over 1 minute to fetal lamb. Note total loss of eye movements during desynchronized electrocorticogram activity and loss of phasic burst activity in nuchal muscle during synchronized electrocortical activity. Hind limb activity was partially suppressed, while diaphragmatic activity remained unaffected. For explanation of abbreviations see legend to Fig. 1.

Table I. Effects of neuromuscular blockade on electrocorticogram activity

	Total time (min)	*Electrocortical pattern*			*No. of cycles*		
		Desynch. (%)	*Mixed (%)*	*Synch. (%)*	*Desynch. (hr^{-1})*	*Mixed (hr^{-1})*	*Synch. (hr^{-1})*
Control	2252	56.5	10.3	33.2	2.3	2.2	2.3
Total neuromuscular blockade	648	39.2	13.9	46.9	3.1	4.0	4.1
Return of diaphragm electromyogram	1696	49.5	20.1	30.3	3.0	3.6	3.0
Return of nuchal electromyogram	2078	52.2	14.0	33.9	2.4	2.7	2.8

Desynch., Desynchronized electrocorticogram pattern; *Synch.*, synchronized electrocorticogram pattern.

With 0.4 mg of *d*-tubocurarine, there was a total loss of nuchal muscle activity during a synchronized electrocorticogram in addition to the loss of eye movements during a desynchronized electrocorticogram. Hind limb activity was partially suppressed, although there was still no effect on diaphragmatic electromyogram activity (see Fig. 3).

Finally, with the highest dose of 0.8 mg, all muscular activity was blocked as indicated by the total quiescence in all electromyogram recordings, including the diaphragm (see Fig. 4). The electrocorticogram, however, continued to cycle between desynchronized, synchronized, and mixed patterns.

From these recordings it can be concluded that there is a difference in the sensitivity of the various muscle groups to *d*-tubocurarine. Fig. 5 illustrates the dose-response curve for percent neuromuscular blockade of the extraocular, nuchal, and diaphragmatic muscles as a function of *d*-tubocurarine dose. These results show that the extraocular muscles are most sensitive to the neuromuscular blocking effect of *d*-tubocurarine, and the diaphragm is the most resistant. Extrapolating from the dose that resulted in 50% blockade, the relative sensitivity of the three muscle groups is as follows; extraocular muscles, 1; nuchal muscle, 2.6; and diaphragm, 6. Thus the extraocular muscles are six times more sensitive to *d*-tubocurarine than the diaphragm.

Fig. 6 illustrates the time course of recovery from total neuromuscular blockade after the highest dose of *d*-tubocurarine (0.8 mg). The top panel is a plot of the percent of animals with 100% blockade as a function of time after *d*-tubocurarine administration. Immediately after drug administration, all animals had complete blockade of the extraocular muscles and of the nuchal and diaphragmatic muscles. By 6 hours later diaphragmatic activity had been recovered in all animals. On the other hand, the extraocular muscles were still completely blocked in 100% of the animals.

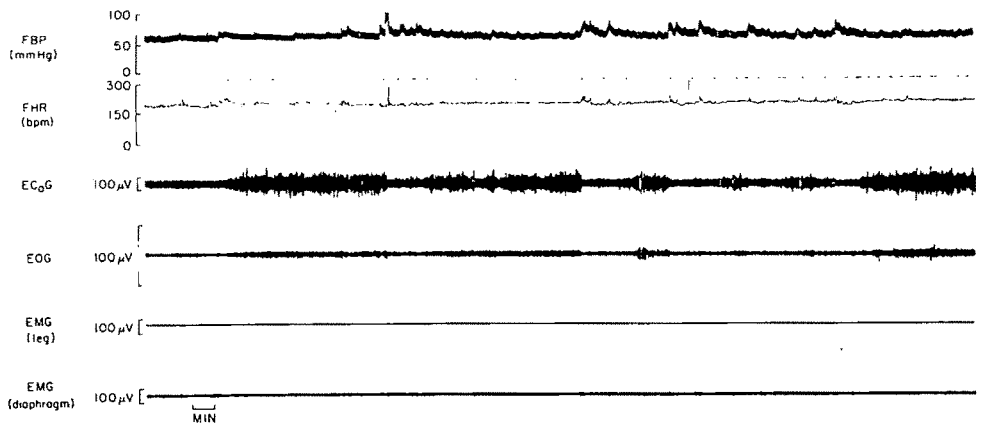


Fig. 4. Polygraphic recording obtained after administration of 0.8 mg of *d*-tubocurarine to fetus. Note total quiescence in all electromyogram recordings. The electrocorticogram, however, continued to show cyclic activity. For explanation of abbreviations see legend to Fig. 1.

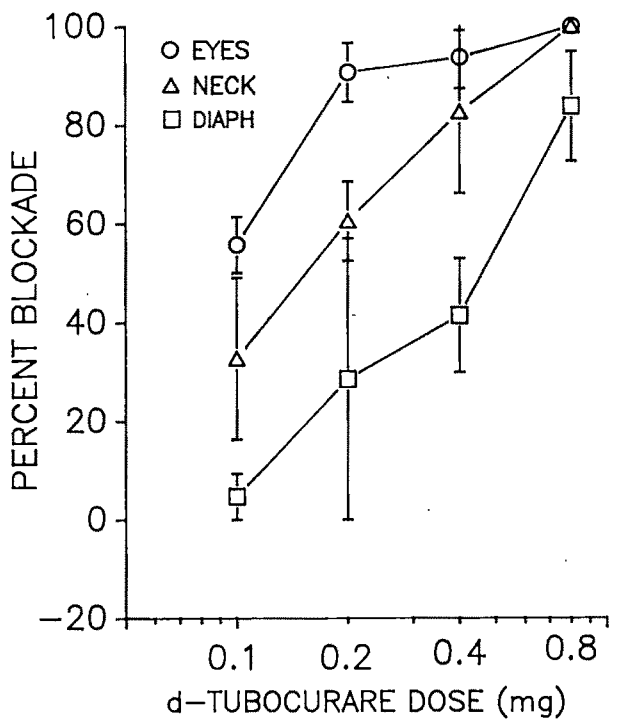


Fig. 5. Dose-response curve showing percent neuromuscular blockade for three muscle groups as function of *d*-tubocurarine dose. ○, Extraocular muscles; △, nuchal muscle; □, diaphragm.

Fig. 7 is a plot of the percent of electromyogram amplitude for the diaphragm and nuchal electromyogram bursts, as well as the percent of control amplitude for eye movements. As a function of time, there is gradual recovery in the electromyogram amplitude of all three muscle groups, with the diaphragm having the fastest recovery. By 8 to 9 hours the diaphragm electromyogram amplitude has completely recovered. On the other hand, neither the nuchal muscles nor the extraocular muscles had completely recovered even by 9 hours after *d*-tubocurarine administration. The order of recovery for the three muscle groups as illustrated by both the quantal (Fig. 6) and graded (Fig. 7) time-action curves is in agreement with the sensitivity of the three muscle groups to the blocking action of *d*-tubocurarine as illustrated by the dose-response curve in Fig. 5.

The effects of neuromuscular blockade on electrocorticogram activity are summarized in Table I. These data were obtained with the two higher doses of *d*-tubocurarine. Data from the two lower doses were not included since they did not result in diaphragmatic paralysis and their effects on the nuchal muscles were very brief. During complete neuromuscular blockade (6 of the 10 animals studied), there was a decrease in desynchronized electrocorticogram activity and an increase in synchronized and mixed activity. Because of the different duration of time at each level of neuromuscular blockade, the number of cycles of each electrocorticogram state was normalized to number per hour. The results showed that the increase in synchronized activity was due to an increase in cycle numbers, while the decrease in desynchronized activity was due to decreased cycle length. With the return of nuchal electromyogram activity, the time distribution pattern in the electrocorticogram was no longer different from that of the control. In two of the animals, nuchal activity had not yet recovered by the end of the experiment.

Table II summarizes the effects of total and partial neuromuscular blockade on fetal blood pressure and fetal heart rate. In the control period fetal heart rate was significantly higher during the mixed and synchronized electrocorticogram cycles ($p < 0.05$); there was no difference in fetal blood pressure during the

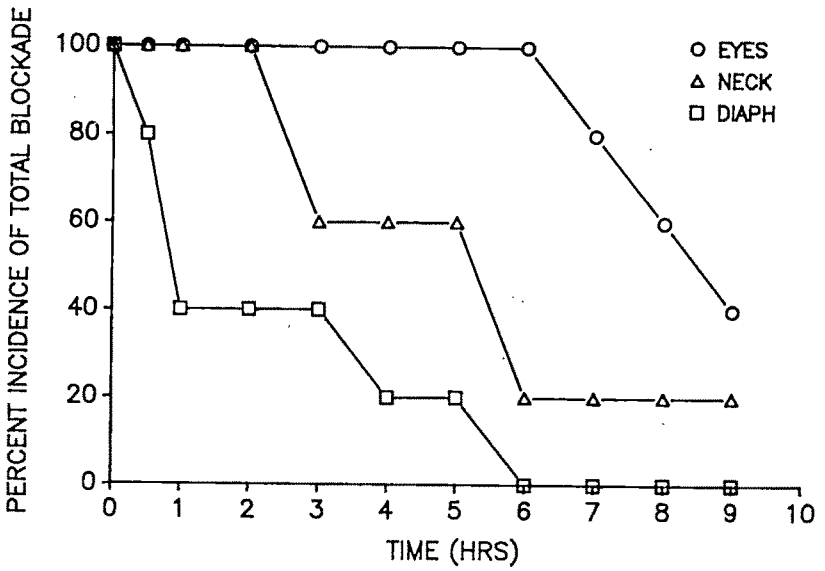


Fig. 6. Time course of recovery from 0.8 mg of *d*-tubocurarine as illustrated by percent of animals with 100% blockade of individual muscle groups as function of time after *d*-tubocurarine administration. ○, Extraocular muscles; △, nuchal muscle; □, diaphragm.

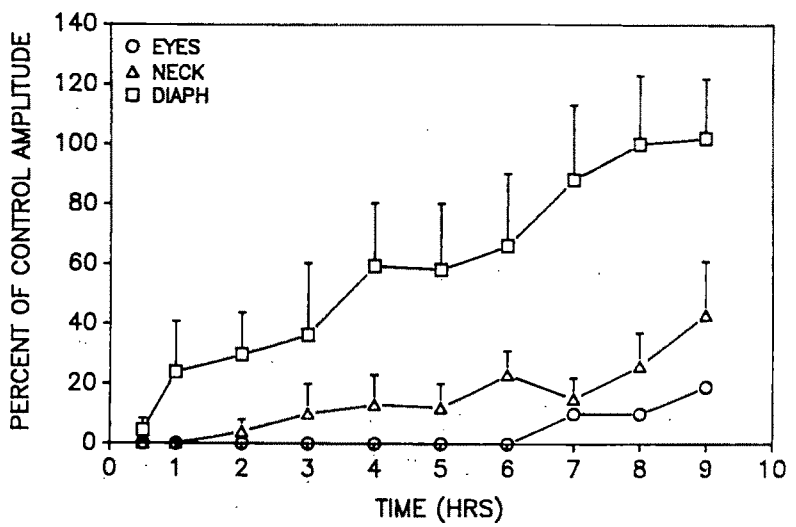


Fig. 7. Time course of recovery from 0.8 mg of *d*-tubocurarine as illustrated by percent of control electromyogram amplitude for three different muscle groups as function of time after *d*-tubocurarine administration. ○, Extraocular muscles; △, nuchal muscle; □, diaphragm.

three electrocorticogram states. During total neuromuscular blockade, there was no change in fetal heart rate during a desynchronized electrocorticogram, but there was a reduction in fetal heart rate in the mixed and synchronized electrocorticogram period, thus resulting in the loss of the heart rate difference between synchronized and desynchronized periods ($p = 0.456$). With the return of nuchal muscle activity, fetal heart rate was higher during a synchronized electrocorticogram than during a desynchronized period, although the difference failed to be statistically significant ($p = 0.091$). Fetal blood pressure did not change with total or partial neuromuscular blockade.

Comment

Previous studies in adult humans and animals demonstrated the relative sensitivity of different muscle groups to the neuromuscular blocking action of *d*-tubocurarine.[6,7] We have found similar differential sensitivities of fetal muscle groups to *d*-tubocurarine. The extraocular muscles were found to be most sensitive, while the diaphragm was the least sensitive. The

Table II. Effects of total and partial NM blockade on fetal heart rate and blood pressure

		Heart rate (beats/min)			*blood pressure (mm Hg)*		
	n	*Desynch.*	*Mixed*	*Synch.*	*Desynch.*	*Mixed*	*Synch.*
Control	10	157 ± 2	169 ± 2*	169 ± 2*	52.4 ± 0.6	53.1 ± 0.8	52.7 ± 0.7
Total neuromuscular blockade	6	157 ± 3	163 ± 3	159 ± 3	53.7 ± 0.8	54.8 ± 0.7	53.0 ± 0.5
Return of diaphragm	10	157 ± 2	159 ± 1	160 ± 2	54.7 ± 0.4	55.3 ± 0.5	53.7 ± 0.3
Return of nuchal electromyogram	8	149 ± 2	153 ± 2	157 ± 2	51.5 ± 0.7	52.7 ± 0.7	51.1 ± 0.6

Desynch., Desynchronized electrocorticogram pattern; *Synch.*, synchronized ECoG pattern.
*$p < 0.05$, when compared with heart rate during desynchronized electrocorticogram in control animals.

twofold difference in sensitivity between the nuchal and hind limb muscles and the diaphragm suggested that it might be possible to select a dose of *d*-tubocurarine that would provide adequate suppression of total body movements with only limited action on the diaphragm.

The duration of action for the different muscle groups is consistent with each respective dose-response curve. After complete neuromuscular blockade with a dose of 0.8 mg of *d*-tubocurarine, the recovery of the nuchal muscles lagged behind that of the diaphragm by almost 4 to 5 hours. Thus monitoring the recovery of peripheral skeletal muscles does not indicate the state of recovery of the diaphragm.

Similar dose-response and time-action studies have not been carried out in the human fetus. Ch. de Crespigny et al.[1] reported that the fetus remained paralyzed for 9 hours after a 3 mg/kg intramuscular dose of *d*-tubocurarine. Subsequently, Moise et al.[3] reported a duration of fetal paralysis of 3.8 hours after 1.5 mg/kg of *d*-tubocurarine. In neither case did the investigators comment on the recovery of diaphragmatic activity. It is possible, at least with the lower dose of *d*-tubocurarine used by Moise et al.,[3] that blockade of the diaphragm may have been limited.

Complete neuromuscular blockade with *d*-tubocurarine was associated with alterations in the cyclic pattern of the fetal electrocorticogram, resulting in an increase in synchronized and mixed activity patterns and shorter cycle durations. As a quaternary ammonium compound, *d*-tubocurarine is highly ionized at plasma pH and is not expected to cross the blood-brain barrier to any appreciable extent. Previous studies have demonstrated that *d*-tubocurarine administered intravenously to the dog or human is not distributed in any significant amount between the blood and the cerebrospinal fluid.[10] Although the blood-brain barrier in the fetal lamb may not be fully developed at this age, we have previously shown that another quaternary compound, methylatropine, does not appear to have any action on central muscarinic sites after intravenous administration.[11] Thus the mechanism of action of *d*-tubocurarine on the fetal electrocorticogram is not clear. However, rather similar electrocorticogram changes also were reported in adult rats given an intramuscular injection of *d*-tubocurarine (0.5 mg/kg). Power spectral analysis revealed an increase in the proportion of δ- and θ-frequencies in subcortical areas and a reduction of all faster frequencies (6 to 15 Hz).[12] These electrocorticogram changes were believed to be due to the stress of immobilization itself rather than a central action of the drug.

The effects of neuromuscular blocking agents on systemic hemodynamic variables in the adult have been reported by a large number of investigators. Intravenous administration of *d*-tubocurarine is associated with marked hypotension, bradycardia, and a redistribution of regional blood flow.[13-15] The hypotension has been reported to result from a combination of autonomic ganglionic blockade,[16] direct myocardial depression,[14] and histamine release.[17] In contrast, we found no significant effect on fetal blood pressure or fetal heart rate even during complete neuromuscular blockade with *d*-tubocurarine. In a recent study Chestnut et al.[8] reported a significant decrease in fetal arterial pressure and a small decrease in fetal heart rate after a slow intravenous infusion of *d*-tubocurarine to fetal lambs. It should be noted that the dose used in their study (3.0 mg/kg) was approximately tenfold higher than the highest dose given in this study. Even at that dose, the reduction in fetal arterial pressure was <10% compared with the control value. Thus it appears that the administration of *d*-tubocurarine to the fetal lamb is not associated with any detrimental hemodynamic effects.

The reason for the lack of a significant hypotensive response to *d*-tubocurarine in fetal lambs is not known. Guyton and Reeder[16] had suggested that in the adult this may be due to the pooling of blood in the capillaries and veins that results from the sudden paralysis and loss of muscle tone. The fetus has a much higher incidence of rapid-eye-movement sleep, which has been shown to be associated with a lack of muscle tone in the postural muscles.[9] In this study *d*-tubocurarine was usually administered during rapid-eye-movement sleep

to ascertain its blocking action on the extraocular muscles and the diaphragm. The lack of muscle tone during the time of *d*-tubocurarine administration may therefore account for the absence of a significant hypotensive response.

The administration of *d*-tubocurarine did, however, result in loss of the cyclic variation in fetal heart rate that has been shown to be associated with cyclic electrocorticogram activity. Fetal heart rate is normally higher during periods of synchronized electrocorticogram activity,[18, 19] and this has been shown to be due to enhanced sympathetic tone.[19] The loss of cyclic variation in fetal heart rate during complete neuromuscular blockade was due to a decrease in fetal heart rate during synchronized electrocorticogram activity, suggesting that the decrease in heart rate with *d*-tubocurarine may be due to autonomic blockade. Our results also showed that the loss of breathing movements during the desynchronized period did not significantly alter fetal heart rate.

In summary, we have shown that fetal muscle groups also demonstrate relative sensitivities to the neuromuscular blocking action of *d*-tubocurarine. Thus it may be possible to select a dose of *d*-tubocurarine that would provide adequate suppression of fetal movements without prolonged paralysis of the diaphragm. Furthermore, we have shown that *d*-tubocurarine results in minimal adverse effects on fetal cardiovascular function even at doses high enough for complete neuromuscular blockade.

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Immunoglobulin G fractions from patients with antiphospholipid antibodies cause fetal death in BALB/c mice: A model for autoimmune fetal loss

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We determined whether purified immunoglobulin G from patients with antiphospholipid antibodies causes fetal loss in pregnant mice. Sera were obtained from nonpregnant parous women (group 1) and nonpregnant women with antiphospholipid antibodies and a history of fetal loss (group 2). Pregnant BALB/c mice were given an intraperitoneal injection of 15 mg of IgG on day 8 of pregnancy. Typically, mice treated with IgG from antiphospholipid antibodies aborted within 48 hours. When animals were sacrificed on days 9 to 15, the uterus of each animal was inspected for the presence of live, dead, or resorbing fetuses. In contrast to mice injected with control IgG or saline solution, each mouse injected with IgG from antiphospholipid antibodies aborted and no live fetuses were found ($p < 0.05$). Histologic examination of the uteroplacental interface showed decidual necrosis in the mice treated with IgG containing antiphospholipid antibodies, and immunofluorescent studies also showed prominent intravascular decidual IgG and fibrin deposition. We conclude that IgG from antiphospholipid antibodies of women with fetal loss causes fetal loss in BALB/c mice. It appears that the fetal loss is mediated by IgG binding in the maternal decidual vasculature. (Am J Obstet Gynecol 1990;163:210-6.)

Key words: Antiphospholipid antibodies, fetal loss, antiphospholipid antibody syndrome, recurrent pregnancy loss

The antiphospholipid antibodies lupus anticoagulant and anticardiolipin are risk factors for thrombosis, recurrent pregnancy loss, and fetal death.[1] These serologic and clinical features constitute what is now known as the antiphospholipid antibody syndrome.[2] The cause of pregnancy loss in patients with the syndrome may be uteroplacental insufficiency stemming from a decidual vasculopathy.[1] However, the exact mechanism of fetal loss is unknown, and in spite of the impressive association with antiphospholipid antibodies, there is no unequivocal evidence that fetal loss is caused by immunoglobulins. The purpose of our investigation is to determine whether purified immunoglobulin G from women with antiphospholipid antibody syndrome causes fetal loss in normal, pregnant mice and to study the mechanism of fetal loss associated with antiphospholipid antibodies.

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Material and methods

Identification of antiphospholipid antibodies. Lupus anticoagulant was identified in plasma by means of the activated partial thromboplastin time as described previously.[3] Plasma samaples showing clotting times beyond 47 seconds were retested after the patient's plasma had been mixed with an equal volume of normal plasma. A diagnosis of lupus anticoagulant was made when this mixture did not correct to within the normal range (normal laboratory mean + 2 SD).

For testing IgG fractions, 0.4 ml of the fraction was mixed with 0.6 ml of pooled normal plasma. The activated partial thromboplastin time was performed on the resulting mixture. Clotting times <48 seconds were considered normal (normal laboratory mean + 2 SD).

The immunoassay for anticardiolipin antibodies was a modification of the enzyme-linked immunoassay method of Loizou et al.[4] and has been described.[3] Each microtiter plate had a standard curve of known positive samples corresponding to those obtained from the Rayne Institute, St. Thomas Hospital, London. Results were expressed in international units of anticardiolipin antibody, and values ≥20 units for IgG or IgM were considered significant.[2]

Patients and control subjects. Women with antiphospholipid antibody syndrome were identified according to the criteria of Harris.[2] Patient 1, a 31-year-

old woman, had two previous pregnancies that ended in fetal death at 22 and 24 weeks' gestation. She had a popliteal vein thrombosis at age 18 after being prescribed oral contraceptives. Patient 2, a 28-year-old woman, had two previous pregnancies; the first ended in fetal death at 26 weeks' gestation and the second was delivered at 25 weeks' gestation because of severe preeclampsia and fetal distress. The infant of the second pregnancy died within 24 hours of delivery. Patient 3, a 36-year-old woman, had three previous pregnancies that ended in fetal death at 19 to 20 weeks' gestation. She had two episodes of pulmonary embolism, each associated with pregnancy. Patient 4, a 25-year-old woman, had two previous pregnancies ending in fetal death at 32 and 24 weeks' gestation, respectively. Patient 5, a 30-year-old woman, had nine successive pregnancy losses, three of which were second-trimester fetal deaths. She also had two thrombotic episodes, one of which was associated with pulmonary embolism.

All patients had lupus anticoagulant and moderately to strongly positive anticardiolipin IgG (i.e., ≥20 IU at 1:50 serum dilution). Repeated determinations for each antiphospholipid antibody had been performed on each patient. No patient had antinuclear antibodies at a titer >1:80 by the indirect fluorescent antibody method with Hep-2 human epithelial cells. Only patient 4 carried a diagnosis of systemic lupus erythematosus, and the disease was in remission at the time her serum sample was obtained. The other women did not have a clinical autoimmune disease.

Normal nonpregnant women aged 20 to 35 with no history of fetal loss, thromboembolism, or autoimmune disease served as controls. None had lupus anticoagulant or anticardiolipin antibodies. Two pooled serum samples were prepared, each consisting of the sera from five different women. Commercially available IgG immune globulin (Sandoz Pharmaceuticals, East Hanover, N.J.) served as an additional control.

Immunoglobulin preparation. Immunoglobulins were precipitated from human plasma or serum with the use of 27.5% ammonium sulfate at saturation. The precipitate was dialyzed against phosphate-buffered saline solution (0.01 mol/L phosphate, pH 7.2), and the IgG fraction was separated by ion-exchange chromatography with diethylaminoethyl cellulose (Pharmacia, Uppsala, Sweden) or affinity chromatography with protein G (Pharmacia). For those fractions separated by ion-exchange chromatography, IgG was further purified by exclusion chromatography with polyacrylamide gel (Sephacryl S-300; Pharmacia). The fractions were dialyzed against phosphate-buffered saline solution and concentrated by anisotropic ultrafiltration. The purity of the IgG was determined by agarose gel electrophoresis; all samples demonstrated a single band of IgG (Fig. 1). The concentration of IgG was determined by a nephelometric method with monoclonal antihuman IgG performed on the Beckman Array System (Beckman Instruments, Brea, Calif.).

Each fraction used in these experiments was tested for endotoxin with a *Limulus* lysate assay (E-Toxate, Sigma Chemical Co., St. Louis). All fractions had <0.5 endotoxin units per milliliter.

Mouse model. Virgin BALB/c (BALB/cAnN; Charles River Laboratories, Wilmington, Mass.) mice were obtained at 10 to 15 weeks of age and maintained in the University of Utah Vivarium with food and water as desired. For mating, previously isolated male animals were placed overnight with previously isolated female animals in a ratio of 1:1. The presence of a coital plug was taken to indicate probable pregnancy (day 1). A diagnosis of pregnancy was confirmed when a mouse achieved a weight gain of ≥12% above her nonpregnant weight by day 8 after coitus.

On day 8 of pregnancy, each animal received a single intraperitoneal injection of 15 mg of IgG, either antiphospholipid antibody IgG or control. The total volume injected was approximately 1 ml, adjusted slightly to ensure an equivalent dose of IgG. We chose to use 15 mg of IgG for these experiments because we had previously found that this dose of antiphospholipid antibody IgG would result in moderate to high levels of anticardiolipin antibodies in mouse serum, mimicking the levels found in women with the antiphospholipid antibody syndrome. Peak activity appeared in the mouse serum on the second day after injection and persisted for 3 to 4 days. The mice were put to death on day 15 of pregnancy or earlier if obvious abortion ensued. For each animal the uterus was inspected under a dissecting microscope for the presence of live fetuses, dead fetuses, or resorptions. About 20% of the mice that were put to death showed no evidence of pregnancy; the uterus was non-pregnant in appearance and had a normal-appearing uterine lining when opened. In questionable cases the presence or absence of pregnancy was determined by histologic examination of the uterus. The nonpregnant animals were excluded from analysis.

The uterus was removed from 17 mice treated with antiphospholipid antibody IgG, five normal IgG-treated mice, and three saline solution controls and fixed in formalin for hematoxylin and eosin staining. Portions of the uterus and kidney from two mice treated with antiphospholipid antibody IgG from two different patients (patients 2 and 3) and one mouse treated with control IgG were snap frozen with liquid nitrogen and stored in OCT compound (Miles Laboratories, Elkhart, Ind.) for immunofluorescent studies. Tissues for immunofluorescent studies were taken 18 to 24 hours after injection of the IgG. Direct immunofluorescent staining for human IgG, fibrinogen, and the third component of complement (C3) was per-

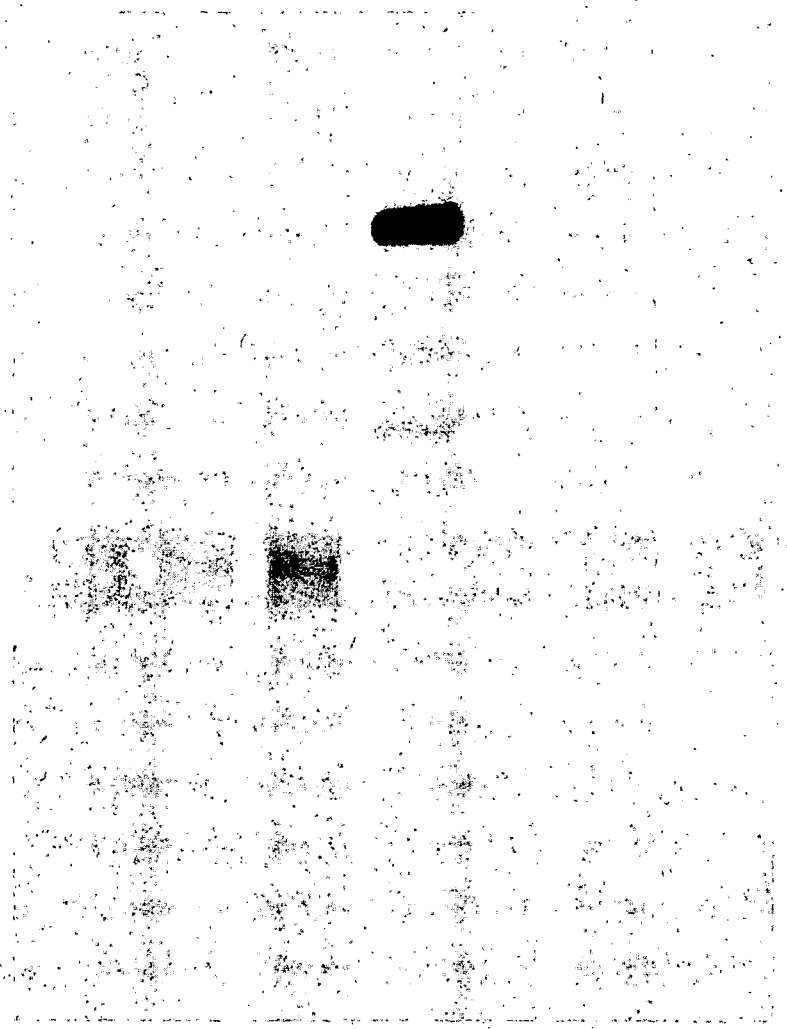


Fig. 1. High-resolution agarose gel electrophoresis of IgG fractions. A sample prepared from pooled control sera is shown in the three lanes on the left. The middle lane is whole normal serum. A sample prepared from the serum of a patient with antiphospholipid antibody syndrome is shown in the three lanes on the right.

formed according to published techniques.[5] Experienced pathologists (T. M. A. or E. H. H.) interpreted the histologic and immunofluorescent preparations in a blinded fashion.

To prove that the low concentrations of endotoxin present in our IgG fractions were not the cause of fetal loss, seven pregnant mice were given endotoxin at doses of 0.5 U (n = 4) or 1.0 U (N = 3) (*Escherichia coli* lipopolysaccharide, Sigma Chemical Co.) by intraperitoneal injection on day 8 of pregnancy. When animals were put to death on day 15 of pregnancy, normal numbers of live fetuses were found in all animals tested.

Results

Table I shows the IgG concentration, activated partial thromboplastin time, and anticardiolipin antibody levels of the IgG fractions prepared for passive immunization of the mice. Although each of the patients with antiphospholipid antibody syndrome had lupus anticoagulant demonstrated on several occasions, only the most concentrated IgG fraction (patient 1), showed a prolonged activated partial thromboplastin time indicative of lupus anticoagulant activity. The failure of the other fractions to demonstrate lupus anticoagulant activity may be due to lower concentrations of IgG, and therefore lupus anticoagulant, in the purified fractions than in the original patient plasmas. Alternatively, lupus anticoagulant activity may be due to an antibody removed by the IgG purification process, such as an IgM. All patients with the syndrome had significant levels of anticardiolipin antibodies measurable in their respective IgG fractions (range 50 to >100 IU). These levels are typical of those found in the sera

of patients with well-defined antiphospholipid antibody syndrome. As expected, all control fractions were negative for lupus anticoagulant and significant levels of anticardiolipin antibodies.

Table II shows the pregnancy outcomes for the IgG-treated mice. Saline solution–injected control animals are included for comparison. The number of live fetuses and resorptions did not differ between the groups treated with control IgG fractions. Furthermore, none of the control groups was statistically different from the mice injected with saline solution. Most important, each of the pregnant mice treated with control IgG fractions had live fetuses found when animals were put to death, with the number of live fetuses ranging from 4 to 10.

In contrast, all mice treated with antiphospholipid antibody IgG had complete fetal loss. Considering the antiphospholipid antibody IgG patient fractions separately, the number of mice with complete fetal loss was significantly different ($p < 0.05$, Fisher's exact test) from that of any control group for fractions from patients 1, 2, and 3. The number of mice treated with the fractions from patients 4 and 5 was too small to achieve statistical significance. Typically, obvious abortion began within 24 to 48 hours of passive immunization. In these cases the animals were put to death immediately. The total number of fetuses present could not be determined with accuracy in these animals because the aborted tissues were lost in the cage or ingested by the mothers. However, in all suspicious cases the presence of trophoblast was confirmed by histologic examination.

Table III shows the results of decreasing doses of antiphospholipid antibody IgG from patient 4. Doses of 1, 2, and 4 mg of the IgG fraction did not result in complete fetal loss. In the five mice treated with 8 mg of IgG, a single fetus was found alive on day 15 of pregnancy. In that same mouse there were seven resorbing fetuses found. In mice treated with doses of the IgG >8 mg, all fetuses were lost.

Twenty-three of the 25 uterine specimens fixed in formalin proved adequate for histologic examination of the uteroplacental junction. Because of obvious abortion, most of the antiphospholipid antibody IgG–treated mice were put to death on days 8 to 10 of pregnancy. At this time in gestation, the trophoblast forms a small portion of the uteroplacental interface, while the decidua is relatively prominent. Moderate to severe decidual necrosis was found in decidua taken from 14 of the 17 mice (82%) treated with antiphospholipid antibody IgG. Moderate or no decidual necrosis was found in the decidua of the five mice treated with control IgG, and no decidual necrosis was found in the decidua of the two saline solution–injected mice.

Direct immunofluorescent studies were performed on tissues from two mice treated with antiphospholipid antibody IgG and a control. The tissues taken from the mouse treated with antiphospholipid antibody IgG from patient 2 stained strongly positive for human IgG (Fig. 2). Staining for fibrin also was positive, while staining for C3 was negative. The uterine tissues taken from the mouse treated with antiphospholipid antibody IgG

Table I. Total IgG concentration, activated partial thromboplastin time, and anticardiolipin antibody levels of IgG fractions

Fraction	*Total IgG (mg/ml)*	*Dilute partial thromboplastin time* (sec)*	*Anticardiolipin antibody level† (IU)*
IgG fractions from patients with antiphospholipid antibody syndrome			
1	20.6	111	>100
2	11.7	27	50
3	18.2	38	>100
4	15.1	33	81
5	15.0	44	79
IgG fractions from controls			
1	12.7	45	<15
2	11.7	43	<15
Commercial IgG	12.0	40	<15

The fractions were prepared from patients with antiphospholipid antibody syndrome and from controls.

*In our coagulation laboratory an abnormally prolonged activated partial thromboplastin time is ≥ 48 seconds, indicating lupus anticoagulant activity.

†A value ≥ 20 IU is considered significant.[2]

Table II. Pregnancy outcome in mice treated with antiphospholipid antibody IgG or control IgG fractions

IgG fraction	*No. of mice*	*Living fetuses*	*Resorptions*
Antiphospholipid antibody IgG			
Patient 1	10	0*	†
Patient 2	7	0*	†
Patient 3	6	0*	†
Patient 4	5	0	†
Patient 5	2	0	†
Controls			
Pooled IgG			
Fraction 1	10	73	6
Fraction 2	7	57	10
Commercial IgG	8	63	6
Saline solution	17	117	10

Mice were put to death on day 15 of pregnancy or earlier if obvious abortion ensued. Saline solution–injected controls (1 ml volume) are shown for comparison

*$p < 0.05$, compared with any control group.

†The total number of fetuses was impossible to determine with accuracy because many of the animals aborted within 48 hours of passive immunization, as evidenced by vaginal bleeding and the passage of tissues in the cage. Because these tissues were often lost or eaten, an accurate count of the number of fetuses could not be performed.

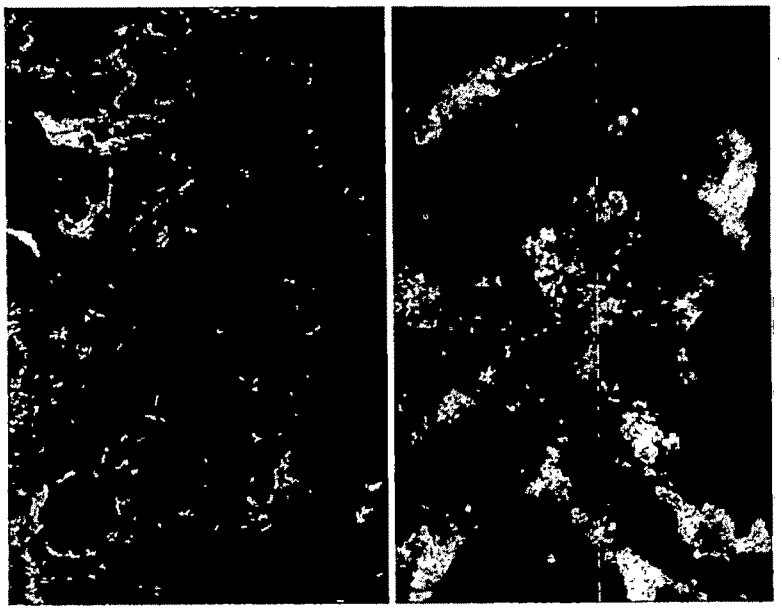


Fig. 2. Antihuman IgG immunofluorescence of mouse decidua. Decidua from a mouse treated with control IgG is shown on the left. (Original magnification × 100.) Decidua from a mouse treated with IgG from a patient with antiphospholipid antibody syndrome is shown on the right at a slightly greater magnification so that the cordlike details of the staining can be appreciated. (Original magnification × 250.)

Table III. Pregnancy outcome with different doses of antiphospholipid IgG fraction

Total IgG administered (mg)	*No. of mice*	*Living fetuses*	*Average live fetuses per mouse*
15	5	0	—
10	3	0	—
8	5	1	<1
4	5	20	4
2	4	21	5.3
1	3	18	6

The mice were treated with different doses of purified IgG from a patient with antiphospholipid antibody syndrome (patient 4). Animals were put to death on day 15 of pregnancy or earlier if obvious abortion ensued.

from patient 3 also were positive for human IgG and fibrin but less so than those taken from the mouse treated with antiphospholipid antibody IgG from patient 2. The cordlike distribution of the immunofluorescence in these decidual tissues strongly suggests intravascular staining. Tissues taken from the mouse treated with control IgG were negative for human IgG, fibrin, and C3.

Comment

Lupus anticoagulant and anticardiolipin antibodies are closely related autoantibodies that bind to phospholipid antigens. Lupus anticoagulant is identified in plasma because it prolongs phospholipid-dependent coagulation tests by binding to the phospholipid portion of the prothrombinase complex.[6] However, the *lupus anticoagulant* is clearly a misnomer because the antibody is associated with thrombosis, not bleeding.[1] Anticardiolipin antibody is identified in plasma or serum by immunoassays that use the phospholipid cardiolipin in the solid phase.[2, 4] There is a strong correlation between moderate to high levels of anticardiolipin antibody and the presence of lupus anticoagulant,[1, 7] and both antibodies are associated with the same clinical features. The risk of antiphospholipd antibody syndrome features probably increases with the level of anticardiolipin antibody.[8]

Fetal loss was first associated with the antiphospholipid antibodies in 1975 when Nilsson et al.[9] reported a case of a woman with lupus anticoagulant, thrombosis, and recurrent fetal deaths. Since then, numerous case reports and series have substantiated the relationship between antiphospholipid antibodies and fetal loss.[10-19] In fact, recent work suggests that antiphospholipid antibodies are the "cause" of pregnancy loss in 5% to 10% of women with recurrent pregnancy loss.[1]

In spite of the strong association with fetal loss, there has been no direct evidence that antiphospholipid antibody, or any other immunoglobulin, is causative. This study, with BALB/c mice, is the first to show that immunoglobulin(s) present in the IgG fraction of women with antiphospholipid antibody syndrome actually causes pregnancy loss. The results of our study are dramatic, with every mouse treated with high doses of

antiphospholipid antibody IgG fraction having complete fetal loss. Dose-response analysis demonstrates that lower doses of IgG fraction containing antiphospholipid antibodies are compatible with fetal survival. Fetal loss in this model does not appear to be due to a type III immune reaction because of the rapid time from treatment to loss and because the control mice did not suffer fetal loss, even after 7 days. Additionally, the fetal loss is not likely due to immune complexes since no complexes were found by high-resolution agarose gel electrophoresis.

There is limited information regarding the pathophysiologic features of antiphospholipid antibody–associated pregnancy loss, all from studies in the human. The fetal losses appear to be caused by a necrotizing decidual vasculopathy associated with decidual necrosis.[1, 10, 19, 20] These events, on the maternal side of the uteroplacental circulation, suggest that the transplacental passage of antibody is not necessary for fetal damage or death. Our findings in mice support the view that the pathophysiologic features of antiphospholipid antibody–associated pregnancy loss are focused on the maternal side of the uteroplacental circulation in the decidua.

In the human the decidual vasculopathy is characterized predominantly by arteriolar fibrinoid necrosis with surrounding decidual necrosis and infiltration of the vascular wall by cells with clear or foamy cytoplasm ("atherosis").[10] Our tissue preparation did not allow a detailed examination of the vasculature because the vessels of the mouse decidua are very small. However, prominent decidual necrosis was observed in more than 80% of the mice treated with antiphospholipid antibody IgG. This finding supports our model for further investigation of antiphospholipid antibody–associated pregnancy loss.

The mechanism by which antiphospholipid antibody IgG might result in decidual vasculopathy is unknown but is presumed to be the same mechanism that results in the high rate of thromboembolic disease in patients with antiphospholipid antibodies. The impressive finding of fibrin deposition in the decidua of two mice treated with antiphospholipid antibodies supports this hypothesis. One authority has proposed that antiphospholipid antibodies cause thrombosis by binding to platelet membranes and promoting platelet activation and aggregation.[21] Patients with antiphospholipid antibody syndrome may have thrombocytopenia, and platelet-associated immunoglobulin is frequently elevated in patients with the syndrome.[21] This proposed mechanism is particularly attractive in the context of our findings because the mouse decidua is rich in intravascular platelets.[22]

In summary, we have shown that purified immunoglobulin(s) from women with antiphospholipid antibody syndrome causes fetal loss in normal pregnant BALB/c mice. In this model, as in the human, decidual necrosis is a feature of fetal loss. Our studies suggest that the necrosis is due to immunoglobulin-mediated intravascular damage with deposition of fibrin clot. In the future our mouse model will be used to explore the pathophysiologic details of fetal loss and to investigate existing and new treatments for pregnancies complicated by antiphospholipid antibodies.

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In vitro effect of RU 486 on sperm-egg interaction in mice

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The effect of RU 486 at different concentrations (1, 5, 10, and 20 μg/ml) was studied on sperm-egg interaction in vitro in B6D2F1 mice. The in vitro fertilization rate of mouse ova decreased from 77.0% (control) to 50.0%, 28.7%, and 7.5% in the presence of RU 486 concentrations at 5, 10, and 20 μg/ml medium, respectively ($p < 0.001$). A concentration of 1 μg/ml did not affect the fertilization rate. A progesterone concentration at equal to or double the concentration RU 486 did not reverse the inhibitory effect of RU 486 on in vitro fertilization, which suggests a progesterone-independent mechanism. Exposure of spermatozoa (for 90 minutes) or ova (for 60 minutes) to RU 486 (20 μg/ml) followed by washing with RU 486–free medium before coincubation did not affect the fertilization rate. The presence or absence of cumulus cells did not change the inhibitory effect of RU 486 (20 μg/ml) on in vitro fertilization. RU 486 at 5 to 20 μg/ml medium was associated with perivitelline polyspermy in nonfertilized ova and enhanced perivitelline polyspermy in fertilized ova. (Am J Obstet Gynecol 1990;163:216-21.)

Key words: RU 486, in vitro fertilization, perivitelline polyspermy, vitellus block

RU 486 [17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)estra-4,9-dien-3-one] is an antiprogestin steroid. At the molecular level, RU 486 is thought to stabilize the complex formed by the progesterone receptor and the heat-shock protein hsp90, which in turn blocks the deoxyribonucleic acid–binding site of the progesterone receptor and precludes a hormonal response.[1] In vitro, RU 486 causes a reduction in the synthesis of human placental chorionic gonadotropin (hCG), human placental lactogen (hPL), and progesterone by syncytiotrophoblast cells.[2] Treatment of rats, mice, and rabbits with RU 486 during early pregnancy blocks decidualization of the endometrium and inhibits implantation.[3,4] Cullingford and Pollard[5] noted complete inhibition of cell proliferation in the mouse uterus by RU 486. Recently, RU 486 has been used as an abortifacient in women.[6,7] It has also been used to enhance cervical ripening[8,9] and to facilitate the delivery of dead fetuses.[10] The antiprogesterone activity of RU 486 has been thought to be responsible for these biologic activities. RU 486 is potentially an important new drug with multiple uses in gynecology. However, the full effect on reproductive function is still being investigated.

This study reports the effects of RU 486 on fertilization in vitro in the mouse.

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Material and methods

Superovulation of mice. Male and female B6D2F1 mice (Charles River Labs., Raleigh, North Carolina) were housed at 23° to 25° C under controlled illumination (14 hours light and 10 hours darkness). Water and pelleted food were supplied at will. Female mice (weight 20 to 25 gm, 7 to 8 weeks old) were superovulated with 7 IU pregnant mare's serum gonadotropin (PMSG) (Sigma Chemical Co., St. Louis) intraperitoneally followed 48 hours later by 7 IU of hCG (Sigma). At 14 hours after hCG injection, mice were sacrificed by cervical dislocation, the oviducts were removed, and cumulus masses were collected in culture medium. Cumulus masses from different mice were pooled and

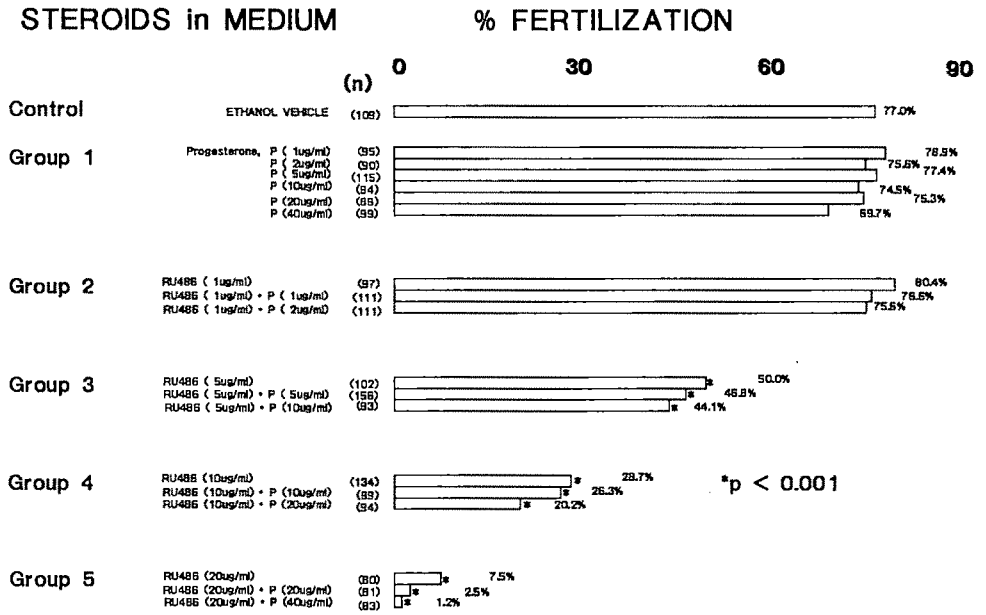


Fig. 1. Effect of RU 486 on in vitro fertilization in mice. The dose-dependent decrease of in vitro fertilization that is shown at concentrations of RU 486 from 5 to 20 μg/ml (groups 2 to 5) is not reversed by equal or double the concentration of progesterone; progesterone (group 1) causes a nonsignificant decrease in fertilization rate.

distributed randomly into 24-cell plates with 0.4 ml of culture medium in each well.

Sperm collection and capacitation. Mature male mice (age >12 weeks) were sacrificed 12½ hours after hCG injection of female mice, and the caudae epididymides were excised. Spermatozoa were released by rupturing the caudae epididymides with fine forceps. Spermatozoa were capacitated for 90 minutes at 37° C in capacitation medium at 5% carbon dioxide and 95% air in a humidified incubator and washed by centrifugation at 800 *g* for 15 minutes before insemination.

In vitro fertilization. Ova (14 to 14½ hours after hCG) were incubated with spermatozoa at a concentration of 100,000 sperm/ml for 3 hours at 37° C at 5% carbon dioxide in a humidified incubator, washed, transferred into culture medium, incubated, and assessed for fertilization after 8 to 10 hours. Embryos were stained with a fluorescent deoxyribonucleic acid–binding dye (Hoechst 33258, Sigma) as previously reported[11] and examined with a fluorescence microscope. The presence of a second polar body, the resumption of second meiotic division, and the presence of a cytoplasmic decondensing sperm head or two pronuclei were considered evidence of fertilization.

Medium. Culture medium consisted of Ham's F-10 (Sigma) supplemented with 3 mg of bovine serum albumin (fraction V, Sigma). Capacitation medium was supplemented with bovine serum albumin 30 mg/ml and equilibrated at 37° C with a 5% carbon dioxide atmosphere for 12 hours before use.

Steroid solutions. RU 486 (Roussel-Uclaf, Raminville, France) and progesterone (Sigma) were solubilized in ethanol. The concentration of ethanol in both treatment and control groups was 0.1%. Since the steroids are lipophilic, medium was not overlaid with oil.

In vitro experiments. The effect of RU 486 on in vitro fertilization was evaluated at concentrations from 1 to 20 μg/ml. Cultures were supplemented with progesterone at concentrations equal to or double the concentration of RU 486. Control cultures of progesterone were evaluated at concentrations from 1-40 μg/ml. Each experiment represents three replicates.

The effect of RU 486 (20 μg/ml) on spermatozoa was evaluated after 90 minutes of exposure in medium. Spermatozoa were washed in RU 486–free medium followed by centrifugation before insemination.

The effect of RU 486 (20 μg/ml) on ova before insemination was evaluated by preincubating the cumulas masses with RU 486 in medium for 1 hour.

The effect of RU 486 (20 μg/ml) on the in vitro fertilization of cumulus-free ova (cumulus treated with 0.1% hyaluronidase, Sigma) and cumulus-enclosed ova was compared.

Data were analyzed by 2 × 2 χ^2 contingency tables.

Results

RU 486 inhibited in vitro fertilization in a dose-response manner in mice at concentrations from 5 to 20 μg/ml (Fig. 1). An RU 486 concentration of 1 μg/ml did not affect fertilization. In vitro fertilization

Table I. In vitro fetilization when gametes were treated with RU 486 before coincubation

Attribute	*% Fertilization*	*n*
Sperm capacitated in presence of RU 486 (20 μg/ml)	77.7	193
Control	71.5	158
Cumulus treated with RU 486 (20 μg/ml) for 1 hr before insemination	78.9	95
Control	80.1	116

Table II. Effect of RU 486 on in vitro fertilization in the presence or absence of the cumulus

Attribute	*% Fertilization*	*n*
Fertilization of cumulus-free ova in presence of RU 486 (20 μg/ml)	5.1%*	78
Control (cumulus-free)	88.0%	75
Fertilization of cumulus-enclosed ova in presence of RU 486 (20 μg/ml)	5.9%†	84
Control (cumulus-enclosed)	82.2	107

The cumulus-free and cumulus-enclosed rates did not differ from each other, nor did the control rates.

*Significantly different from control (cumulus-free) ($p < 0.001$).

†Significantly different from control (cumulus-enclosed) ($p < 0.001$).

rates of mouse ova decreased from 77.0% (control) to 50.0%, 28.7%, and 7.5% in the presence of RU 486 concentrations at 5, 10, and 20 μg/ml medium, respectively. Progesterone (1 to 40 μg/ml) did not significantly affect fertilization in vitro (group 1, Fig. 1), although there was a consistent nonsignificant decrease in fertilization rates noted in all experimental groups in the presence of progesterone at higher concentrations. The addition of progesterone at equal to or double the concentration of RU 486 did not reverse the inhibitory effect of RU 486 at 5 μg/ml (group 3), 10 μg/ml (group 4), or 20 μg/ml (group 5) on in vitro fertilization (Fig. 1).

Spermatozoa capacitated in the presence of RU 486 for 90 minutes at a concentration of 20 μg/ml followed by washing in RU 486–free medium did not alter the fertilization capability of the spermatozoa compared with that of control spermatozoa capacitated in RU 486–free medium (Table I). Likewise, exposure of ova to RU 486 (20 μg/ml) before insemination followed by washing of the ova in RU 486–free medium did not alter the quality of ova as reflected by fertilization (Table I).

The presence or absence of cumulus cells did not alter the inhibitory effect of RU 486 on in vitro fertilization (Table II). The fertilization rate of either cumulus-free or cumulus-enclosed ova in the presence of RU 486 (20 μg/ml) was significantly depressed compared with fertilization in RU 486–free medium ($p < 0.001$) but was not significantly different (5.12% vs 5.95%) between each other (cumulus-free vs cumulus-enclosed).



Fig. 2. Perivitelline polyspermy in unfertilized ova under the influence of RU 486 (20 μg/ml). Three spermatozoa and the first polar body are visible in perivitelline space; two spermatozoa are attached to zona pellucida.

In ova that did not fertilize in the presence of RU 486, there was a progressive increase in the number of spermatozoa with increased concentrations of RU 486 that had penetrated the zona pellucida but not the vitelline membrane. Frequently, multiple spermatozoa (one to nine) collected in the perivitelline space (Fig. 2). No sperm were noted in the perivitelline space of control ova, which did not fertilize in RU 486–free medium (Fig. 3). There were no sperm in the perivitelline space in ova that did not fertilize in the presence of RU 486 at a concentration of 1 μg/ml. The number of unfertilized ova with multiple spermatozoa in the perivitelline space increased from 0.0% (control) to 58.8% at 5 μg/ml, 75.0% at 10 μg/ml, and 72.9% at 20 μg/ml concentrations of RU 486 ($p < 0.001$, Fig. 3).

Perivitelline polyspermy among fertilized ova increased from 10.7% (control) to 54.9%, 73.6%, and 83.3% at RU 486 concentrations of 5, 10, and 20 μg/ml, respectively ($p < 0.001$, Fig. 4). From one to eight sperm collected in the perivitelline space of fertilized ova. An RU 486 concentration at 1 μg/ml did not affect the perivitelline polyspermy in fertilized ova.

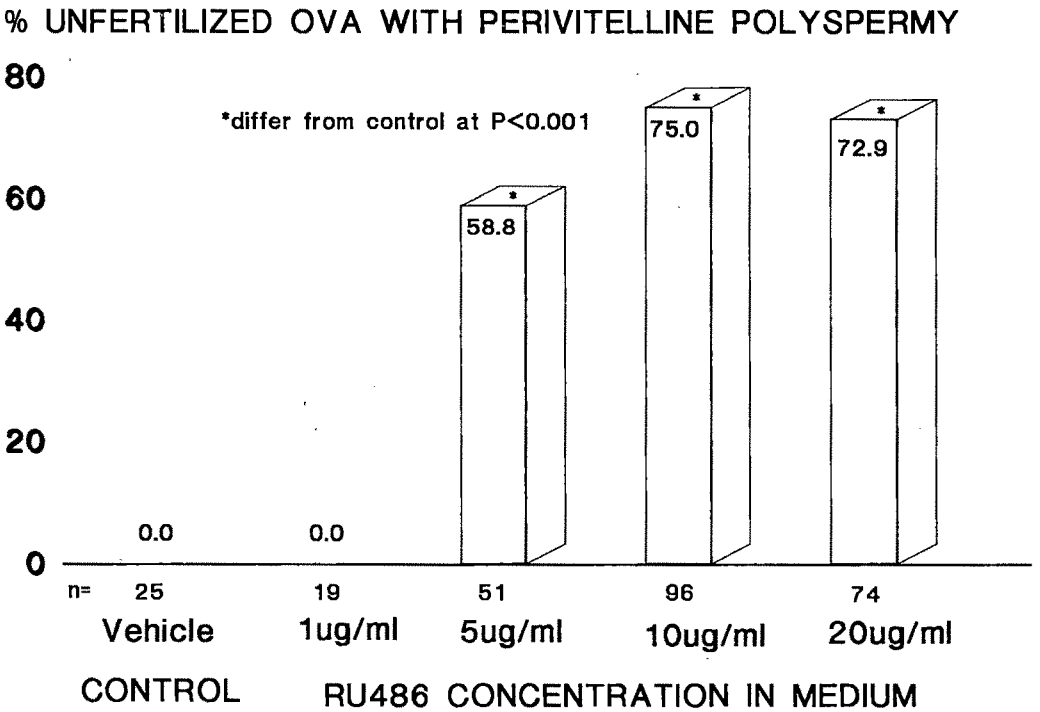


Fig. 3. A dose-dependent increase in perivitelline polyspermy is noted in unfertilized ova under the influence of RU 486.

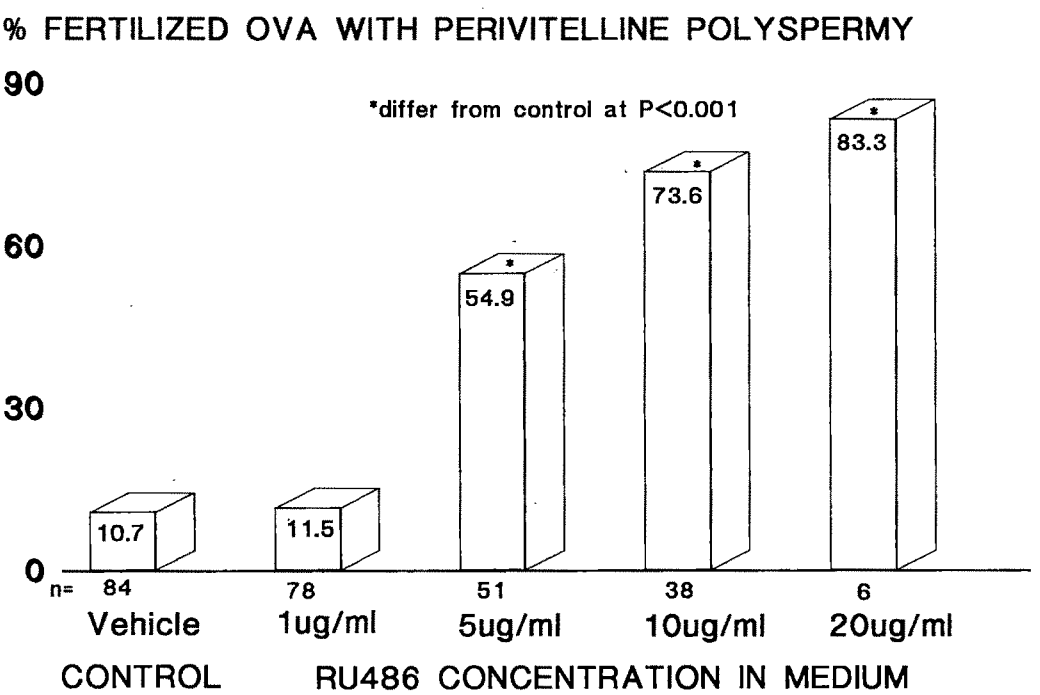


Fig. 4. A dose-dependent increase in perivitelline polyspermy is noted in fertilized ova under the influence of RU 486.

Comment

The presence of RU 486 resulted in a dose-dependent decrease in fertilization of mouse ova in vitro. The effect does not appear to result from a toxic effect on either the spermatozoa or ova alone, since the exposure of spermatozoa or ova to RU 486 (sperm 90 minutes; ova 60 minutes) followed by washing did not decrease the in vitro fertilization rate even

at a concentration of 20 μg/ml. It was necessary for RU 486 to be present during coincubation of ova and spermatozoa before fertilization was noted to decrease. Concentrations of ≥5 μg/ml were necessary to demonstrate the inhibitor effect of RU 486 on in vitro fertilization. The inhibitory effect of RU 486 on in vitro fertilization could not be reversed by the presence of progesterone at equal to or twice the concentration (in micrograms per milliliter) of RU 486. Most of the biologic effects of RU 486 are thought to be mediated through its antiprogestin action. However, the lack of reversibility of RU 486 on the inhibition of in vitro fertilization in the presence of progesterone suggests that either the inhibition of fertilization is mediated through a progesterone-independent mechanism or the binding of RU 486 to the progesterone receptor is nonreversible in the presence of progesterone at equal to or double the concentration used in this study. The inhibitory effect of RU 486 on human syncytiotrophoblast production of hCG, hPL, and progesterone has previously been reported to be reversed by the addition of exogenous progesterone.[2] However, a lower concentration of RU 486 than in our study was used to support syncytiotrophoblast hormone production, and a tenfold concentration of progesterone was used to reverse the inhibitory effect.[2]

In humans, RU 486 has been shown to inhibit granulosa cell progesterone production.[12] Progesterone, however, has not been shown to be necessary for fertilization in vitro. In fact, in this study we noted a tendency for decreased fertilization at high progesterone concentrations. However, this trend was not statistically significant. In this study RU 486 inhibited fertilization in the presence or absence of cumulus cells (Table II).

In mice and several other species, including the human and hamster, acrosome-intact capacitated sperm bind to a glycoprotein (ZP3) on the surface of the zona pellucida.[13-16] ZP3 induces the acrosome reaction, and only acrosome-reacted spermatozoa are capable of penetrating the zona pellucida and binding to the vitelline membrane.[17] Penetration of the vitelline membrane by a sperm results in fusion of the cortical granules with the plasma membrane and release of their contents (cortical reaction). Degradation of cortical granules results in the zona reaction, which in turn blocks polyspermy. However, in some strains of mice, even after the first sperm fuses with the vitelline membrane, a few additional spermatozoa continue to enter the perivitelline space.[18] Sato[18] noted penetration of the zona pellucida by one to eight spermatozoa even after a sperm had fused with the vitellus. Perivitelline polyspermy is not uncommon. In Sato's study[18] a total of 47 accessory spermatozoa were noted in the perivitelline space in 24 eggs. Most of the spermatozoa had entered the perivitelline space within 1 minute after fusion of the fertilizing sperm with the vitellus.[18] In this study we noted a dose-dependent increase in the number of unfertilized ova and zygotes with perivitelline polyspermy in the presence of RU 486. The block of polyspermic fertilization in the mouse is thought to be at the level of the zona.[19] Polyspermic fertilization occurs when capacitated and acrosome-reacted sperm successfully penetrate the zona and fuse with the vitellus. In the presence of RU 486 at concentrations of ≥5 μg/ml, multiple spermatozoal penetration of the zona occurs. However, despite the presence of multiple spermatozoa in the perivitelline space, polyspermic fertilization with penetration of the vitellus did not occur in this study. Perivitelline polyspermy was noted in 10.7% of control zygotes (Fig. 4). However, perivitelline polyspermy increased dramatically in the presence of RU 486. There was no significant difference in the degree of polyspermy in fertilized and unfertilized ova.

One possible explanation for the data presented is a block of the zona reaction in fertilized mouse ova in the presence of RU 486 that allows spermatozoa to accumulate in the perivitelline space despite fertilization. RU 486 at higher concentrations might cause inhibition of penetration of the vitelline membrane but not the zona pellucida. Another possibility is that RU 486 enhances zona penetration by spermatozoa.

The presence of multiple spermatozoa in the perivitelline space, even in unfertilized ova, also was noted at concentrations of RU 486 of 5 to 20 μg/ml. Since no sperm had penetrated the plasma membrane and fertilized the ova, the release of the cortical granules and the zona reaction should not have occurred. However, RU 486 appears to allow spermatozoa to penetrate the zona but not the vitelline membrane, thereby resulting in perivitelline polyspermy but not fertilization. No zona penetration was noted in unfertilized ova in the absence of RU 486 or at a concentration of 1 μg/ml. Whether spermatozoa that penetrate the zona under the influence of RU 486 are acrosome-reacted is under investigation.

In conclusion, RU 486 inhibits fertilization in vitro in a dose-dependent manner that is not reversed by twice the concentration of progesterone. The decreased fertilization does not appear to result from a toxic effect on either the ova or spermatozoa and is independent of the presence of surrounding granulosa cells. Perivitelline polyspermy occurs in unfertilized and fertilized eggs in the presence of RU 486.

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Relationship between the ovine fetal umbilical artery blood flow waveform and umbilical vascular resistance

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Ultrasonic umbilical artery blood flow velocity waveform indexes decrease throughout gestation as umbilical blood flow increases. However, it is not known whether the decrease in indexes such as systolic/diastolic ratio is a direct result of a change in umbilical vascular resistance. Umbilical artery blood flow was measured as vasoactive agents angiotensin II, arginine vasopressin, norepinephrine, serotonin, and the thromboxane A_2 sympathomimetic agent U-46619 were infused into the inferior vena cava of chronically instrumented ovine fetuses. Angiotensin II, arginine vasopressin, norepinephrine, serotonin, and U-46619 all significantly increased fetal arterial pressure levels. Angiotensin II, arginine vasopressin, and U-46619 significantly reduced umbilical blood flow and fetal heart rate. All five pressor agents increased umbilical vascular resistance. Systolic/diastolic ratios were obtained from pulsatile umbilical blood flow tracings. Systolic/diastolic ratios before infusions were significantly correlated with baseline values of umbilical blood flow ($r = -0.55$) and umbilical vascular resistance ($r = 0.52$). Systolic/diastolic ratios decreased with increasing infusion rates of angiotensin II, arginine vasopressin, norepinephrine, and serotonin, and increased with infusion of U-46619. There was no significant correlation between systolic/diastolic ratio and either umbilical blood flow or umbilical vascular resistance during infusion of angiotensin II, arginine vasopressin, or serotonin. Systolic/diastolic ratio decreased with increasing umbilical vascular resistance during norepinephrine infusion ($r = -0.44$). Systolic/diastolic ratio changed in the predicted direction only when umbilical vascular resistance was increased by infusion of U-46619 ($r = 0.80$). We conclude that umbilical artery waveform analysis is not an adequate predictor of acute changes in umbilical blood flow or vascular resistance. (Am J Obstet Gynecol 1990;163:222-9.)

Key words: Pregnant ewe, Doppler ultrasonography, gestation

Measurement of umbilical artery blood flow velocity waveform indexes such as systolic/diastolic (S/D) ratio has been proposed as a means to noninvasively assess fetal well-being. Umbilical blood flow velocity waveform indexes decrease throughout gestation as umbilical blood flow increases and umbilical vascular resistance decreases.[1] It has been proposed that the decrease in S/D ratio is a result of a progressive increase in the size of the fetoplacental vascular bed and decreasing vascular resistance.[2] It is not known whether changes in waveforms are caused by changes in umbilical vascular resistance or whether another factor, such as increased number of vessels in the fetoplacental microcirculation, that may lead to decreases in both S/D ratio and umbilical vascular resistance, is responsible for the correlation between S/D ratio and umbilical vascular resistance.

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Pathologic studies have indicted a strong relationship between waveform indexes and the number of small vessels in the placental vascular bed.[3, 4] The relationships between S/D ratio, umbilical vascular resistance, and the size of the fetoplacental vascular bed might be clarified by procedures that alter either umbilical vascular resistance or the number of fetoplacental microvessels with blood flow. Experiments with the use of embolization of the umbilical circulation with microspheres, thereby decreasing the functional size of the fetoplacental vascular bed, have not clarified these relationships.[5, 6] During a series of embolizations over a short period of time S/D ratio and umbilical vascular resistance were highly correlated,[5] whereas during a 9-day schedule of daily embolization changes in S/D ratio and umbilical vascular resistance occurred at different rates.[6] Alteration of umbilical vascular resistance pharmacologically has not clarified these relationships. Infusion of U-46619, a thromboxane A_2 sympathomimetic, into the lower aorta of sheep fetuses increased vascular resistance of the umbilical cotyledonary circulation and increased S/D ratio, whereas infusion of prostacyclin decreased S/D ratio but did not significantly alter cotyledonary vascular resistance.[7]

Previously, with the use of high frequency measurements of umbilical blood flow by means of transit-time

Doppler flow probes, we showed that S/D ratio and umbilical blood flow change with gestation in the chronically instrumented ovine fetus in a manner similar to that ascribed to human fetuses.[1] We also showed that in the ovine fetus S/D ratio and umbilical blood flow are highly correlated throughout the last trimester. In the present investigation we measured umbilical blood flow and fetal arterial pressure in chronically instrumented ovine fetuses during intravenous infusion of vasoactive agents to determine whether acute increases in umbilical vascular resistance are accompanied by increases in umbilical S/D ratios.

Methods

Surgical procedures. Nine pregnant ewes (40 to 60 kg) carrying singleton (seven) or twin (two) fetuses were instrumented during aseptic surgical procedures. Guidelines approved by the University of Cincinnati for the care and use of the animals were followed. Maternal and fetal instrumentation was performed at 105 to 110 days' gestation. In the two cases of twin pregnancies, only one fetus was instrumented. Ewes were fasted for 48 hours before surgery. On the day of surgery a diazepam preparation (Valium, 10 mg) was injected intramuscularly 30 minutes before intravenous administration of pentobarbital (15 mg/kg). Surgery was performed under pentobarbital and spinal (Pontocaine, 12 mg) anesthesia. Polyvinyl catheters were placed in the maternal distal aorta and inferior vena cava through the left femoral artery and vein. The uterus was then exposed by means of a midline incision. Through a small uterine incision, the left fetal hind limb was delivered to place polyvinyl catheters into the fetal aorta through the femoral artery and the inferior vena cava through a fetal hind limb vein. The volumes of all catheters were determined before placement.

After a left retroperitoneal incision, the fetus was marsupialized to the uterus. The area surrounding the common umbilical artery was exposed, and a 6 to 8 mm ultrasonic transit-time flow probe (Transonic Systems, Inc., Ithaca, N.Y.) was placed around the common umbilical artery, just proximal to the branches of the umbilical artery. At this location, approximately 95% of the blood flow is directed to the fetoplacental circulation. Fetal and uterine incisions were subsequently closed. Electromagnetic flow probes (Dienco, Los Angeles) were placed around both maternal middle uterine arteries. All instrumentation was passed through a subcutaneous tunnel and exteriorized through a small incision on the ewe's left flank. Catheters were flushed and filled with heparinized saline solution (1000 U/ml, maternal; 500 U/ml, fetal). Catheters and cables were kept in a canvas pouch attached to the ewe's left flank. Catheters were flushed every other day with heparinized saline solution at the above concentrations. Antibiotics were administered to the ewe and fetus. The ewe received 6 ml of Combiotic intramuscularly (Pfizer, New York) postoperatively and 6 ml doses for 3 days after surgery. The fetus received 1 gm of ampicillin (Omnipen, Wyeth, Philadelphia) through an amniotic fluid catheter postoperatively and 0.5 gm for 3 days after surgery.

Measurements. Hemodynamic recordings were made on sheep ranging from 110 to 129 days' gestation. On the experimental day sheep were allowed a period of acclimatization to experimental rooms, after which baseline measurements were obtained for 30 minutes. Vasoactive agents were dissolved in saline solution at different concentrations, each 10-fold greater than the other. Different infusion rates of the vasoactive agents could then be delivered through the fetal hind limb vein catheter with only two different infusion rates (either 0.10 or 0.30 ml/min) by an infusion pump (model 355, Sage Instruments, Cambridge, Mass.). Fetal body mass was estimated from growth curves generated in our laboratory as:

$$\text{Fetal body mass (gm)} = [(\text{Days of gestation} - 37) \cdot 0.16]^3$$

Different doses of the vasoactive substances were infused into the fetal hind limb vein in ascending order for a period of 5 minutes after the venous catheter was filled with the appropriate solutions and volume. All experiments were performed on animals with fetal $P_aO_2 \geq 18$ mm Hg and pH ≥ 7.3. Five different vasoactive substances were infused. Only one substance was used on a given day on any given sheep. The substances included angiotensin II at infusion rates of 0.1, 0.3, 1, and 3 μg/min/kg (Ciba Pharmaceuticals, Summit, N.J.); arginine vasopressin acetate at infusion rates of 1, 3, 10, 30, 100, and 300 ng/min/kg (Sigma Chemical Co., St. Louis); norepinephrine bitartrate at infusion rates of 0.3, 1, and 3 μg/min/kg (Sigma); serotonin at infusion rates of 1, 3, and 10 μg/min/kg (Sigma); and the thromboxane A_2 sympathomimetic agent U-46619 at infusion rates of 0.3, 1, 3, and 10 μg/min/kg (Cayman Chemical Co., Ann Arbor, Mich.). Complete dose-response relationships were obtained on four sheep for angiotensin II, two sheep for arginine vasopressin, three sheep for norepinephrine, three sheep for serotonin, and three sheep for U-46619.

Both pulsatile and integrated umbilical artery blood flow were recorded with model T101 Doppler ultrasonographic flowmeters (Transonic). Blood pressure was recorded with MP 15 pressure transducers (Micron Instruments, Inc., Simi Valley, Calif.) anchored at the level of the maternal sternum and attached to maternal and fetal arterial catheters. Heart rate was derived from the arterial pressure pulse by means of Sensor Medics 9857 cardiotachometer couplers (Anaheim, Calif.).

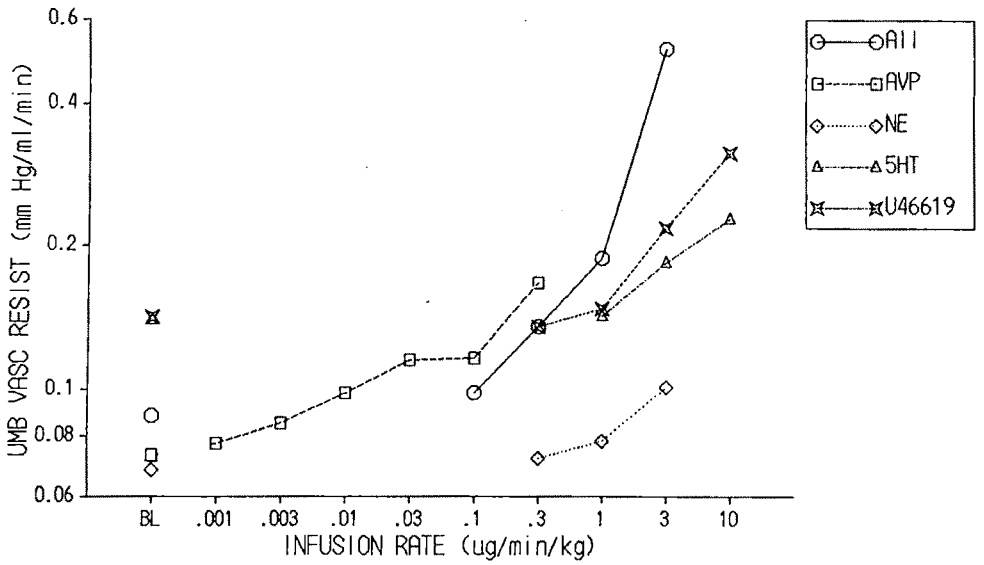


Fig. 1. Umbilical vascular resistance during infusion of angiotensin II (*AII*) ($n = 4$), arginine vasopressin (*AVP*) ($n = 2$), norepinephrine (*NE*) ($n = 3$), serotonin (*5HT*) ($n = 3$), and U-46619 ($n = 3$). All five substances significantly increased umbilical vascular resistance ($p < 0.05$). Values are means at each infusion rate plotted on log scale. Error bars are omitted for clarity.

Umbilical blood flow, fetal arterial pressure, fetal heart rate (FHR), maternal arterial pressure, maternal heart rate, and right and left uterine blood flows were recorded continuously with SensorMedics R612 recorders. Because the experiments were all conducted before the last 2 weeks of pregnancy, we did not measure amniotic fluid pressure. Therefore, vascular resistance was computed from only mean umbilical blood flow and fetal mean arterial pressure measured from the aorta, neglecting venous and amniotic pressures. Hemodynamic responses to arginine vasopressin infusion have been previously reported.[8]

Waveform analysis. Umbilical blood flow was recorded at the speed of 25 mm/second. Pulsatile recordings were obtained by setting the low-pass cutoff frequency of the flowmeter to either 30 or 100 Hz for at least 1 minute. Blood flow was also recorded at 0.1 Hz to determine umbilical blood flow averaged over the cardiac cycle. Peak systolic and minimum diastolic values were measured across a period of at least 10 to 15 seconds (10 to 20 cardiac cycles) during which systolic and diastolic values did not vary by more than 20%. S/D ratio was computed as maximum divided by minimum value of the flow wave.

Statistical analysis. Values reported were obtained near the end of the 5-minute infusion periods. In general, parameters reached a steady state during the last 2 minutes and a single value averaged over the last 2 minutes for each parameter and infusion rate in each animal was used for statistical analysis. One factor analysis of variance with repeated measures across different infusion rates of each vasoactive substance was used to determine whether any differences existed in responses to different infusion rates. Newman-Keuls posthoc analysis was then used to determine which groups were significantly different from each other ($p < 0.05$). Because values of S/D ratio may significantly differ from a gaussian distribution,[9] statistical analyses involving S/D ratio were also performed with the resistance index (RI) as RI = (systolic − diastolic)/systolic value of the waveform, the distribution of which appears to be gaussian.[9] These indexes are exactly related by the relationship RI = 1 − S/D ratio^{-1}. In this investigation S/D ratio and RI had a linear correlation coefficient of 0.97. The distribution of S/D ratio values was significantly skewed in the positive direction (skewness = 0.75, $p < 0.01$), but the distribution of RI values showed no evidence of skewness (skewness = − 0.11) and neither distribution showed any evidence of kurtosis. Results of analyses based on either S/D ratio or RI led to the same conclusions and only the S/D ratio data are shown here.

Results

No maternal hemodynamic changes were observed during infusion of any of the five vasoactive substances used in this investigation. The vasoactive agents that we infused into the fetal hind limb vein all produced dose-related increases in fetal arterial pressure ranging from 24% to 52% with different agents. Angiotensin II, arginine vasopressin, and U-46619 produced dose-related decreases in umbilical blood flow. Maximum

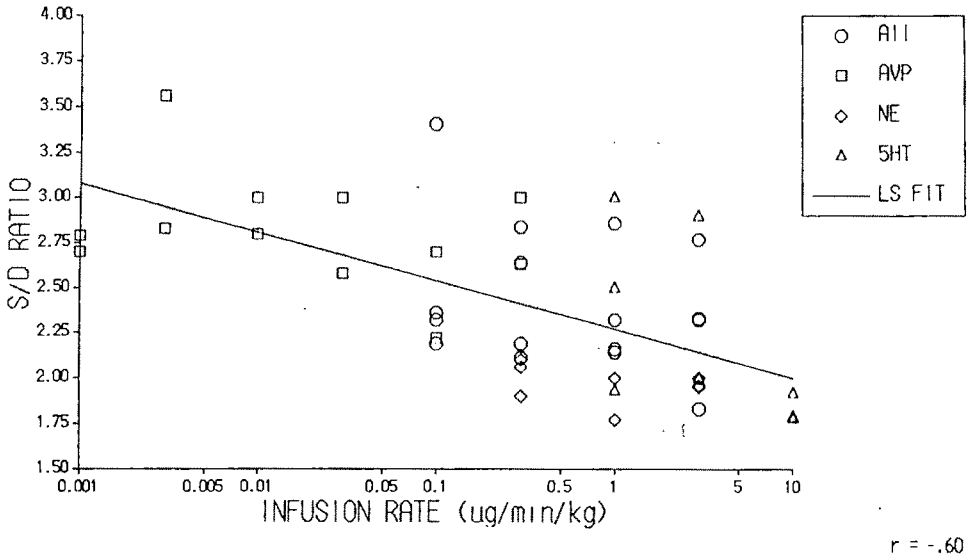


Fig. 2. Relationship between S/D ratio and infusion rate of angiotensin II (*AII*) ($n = 4$ sheep · 4 doses), arginine vasopressin (*AVP*) ($n = 2$ sheep · 6 doses), norepinephrine (*NE*) ($n = 3$ sheep · 3 doses), and serotonin (*5HT*) ($n = 3$ sheep · 3 doses). S/D ratio decreased significantly with increasing infusion rate ($r = -0.60$, $n = 46$, $p < 0.01$). Line is least squares fit of data.

decreases were 74%, 34%, and 34%, respectively. FHR also decreased with infusion of angiotensin II, arginine vasopressin, and U-46619 by a maximum of 15%, 42%, and 37% with these three agents, respectively. No significant changes in umbilical blood flow or FHR could be observed with infusion of norepinephrine or serotonin. All five agents significantly increased umbilical vascular resistance in a dose-related fashion (Fig. 1). Because of the number of observations, clear relationships between dose and S/D ratio for each pressor agent could not be shown. However, by pooling the data from angiotensin II, arginine vasopressin, norepinephrine, and serotonin, a significant correlation between S/D ratio and log infusion rate could be observed ($r = -0.60$, $p < 0.01$) (see Fig. 2).

Before infusion of vasoactive agents the baseline S/D ratios that we recorded were significantly correlated to both umbilical blood flow ($r = -0.55$, $p < 0.01$) (Fig. 3) and umbilical vascular resistance ($r = 0.52$, $p < 0.01$) (Fig. 4). S/D ratio changed as would be expected if S/D ratio were a predictor of umbilical vascular resistance only during infusion of the thromboxane A_2 sympathomimetic agent U-46619; S/D ratio increased as umbilical vascular resistance increased ($r = 0.80$, $p < 0.01$) (Fig. 5, *E*). However, S/D ratio did not increase as umbilical vascular resistance increased during infusion of the other four vasoactive agents. There was no correlation between S/D ratio and umbilical vascular resistance during infusion of angiotensin II, arginine vasopressin, or serotonin (Fig. 5, *A, B, C,*), and during infusion of norepinephrine, S/D ratio decreased as umbilical vascular resistance increased ($r = -0.44$, $0.05 < p < 0.10$) (Fig. 5, *D*). During these acute changes in umbilical vascular resistance, the relationship between S/D ratio and umbilical vascular resistance observed before infusions was not maintained for all five pressors.

Umbilical artery waveform values have been shown to be inversely correlated to FHR, at least within a range of FHRs.[1, 10, 11] Overall, in the present investigation S/D ratio was also significantly correlated to heart rate ($r = -0.38$, $p < 0.5$), although the relationship differed with infusion of different drugs. Correlation coefficients between S/D ratio and heart rate were -0.09, 0.02, -0.38, -0.22, and -0.39 for angiotensin II, arginine vasopressin, norepinephrine, serotonin, and U-46619, respectively. None of these correlation coefficients reached a significance level of $p < 0.05$ for the number of observations. The effect of heart rate on S/D ratios did not appear to affect the relationship between umbilical vascular resistance and S/D ratio. Analysis by multiple linear regression with the use of both heart rate and vascular resistance as predictors of S/D ratio did not reveal any significant relationships except for U-46619 ($r^2 = 0.46$). This value was similar to that found for umbilical vascular resistance alone. Moreover, heart rate and umbilical vascular resistance were significantly related to each other during infusion of the vasoactive substances, substantially reducing the validity of this analysis. Heart rate decreased as umbilical vascular resistance increased during infusion of angiotensin II, arginine vasopressin, and U-46619

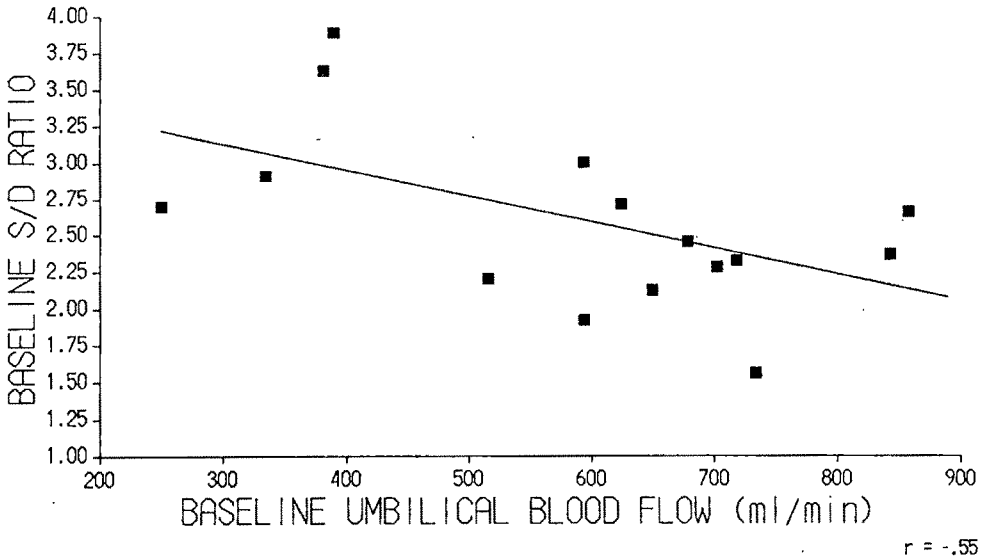


Fig. 3. Relationship between baseline S/D ratio and baseline umbilical blood flow before infusion of vasoactive substances. S/D ratio was significantly related to umbilical blood flow ($r = -0.55$, $n = 15$, $p < 0.05$). Line is least squares fit of data.

($r = -0.68, -0.67$, and -0.71, respectively, $p < 0.05$), and heart rate increased as vascular resistance increased during infusion of norepinephrine ($p < 0.05$) and serotonin ($0.05 < p < 0.1$), ($r = 0.72$ and 0.47, respectively).

Comment

In the present investigation we sought to determine whether the magnitude of a standard velocity waveform index (S/D ratio) is related to fetal umbilical vascular resistance by directly measuring umbilical blood flow and arterial pressure in the chronically instrumented ovine fetus while increasing umbilical vascular resistance by infusion of vasoactive substances. The present study allows accurate measurement of fetoplacental blood flow and umbilical vascular resistance at the same time that blood flow waveforms are obtained. Previously, we performed waveform analysis on umbilical blood flow recordings obtained from implanted transit-time Doppler flow probes and showed that progressive increases in umbilical blood flow during gestation are accompanied by decreasing S/D ratios.[1] We also showed that the waveforms that we record from sheep convey essentially the same information as waveforms obtained externally from human beings. In our previous investigation we computed three different waveform indexes (S/D ratio, resistance index, and pulsatility index).[1] We found that all three indexes correlate very highly with each other ($r = 0.90$ to 0.98). This correlation has been reported previously for externally measured velocity waveforms of human beings.[9] Therefore, in this study we computed only S/D ratio.

The decrease in S/D ratio with gestation is often attributed to progressively greater vascularization and diminishing vascular resistance in the fetoplacental circulation.[2] Support for this hypothesis comes from pathologic correlations. Giles et al.[3] reported that abnormal waveforms occur in association with sclerosis and obliteration of tertiary villus arterioles, and McCowan et al.[4] found a significant negative correlation ($r = -0.71$) between waveform index and the number of small arterioles observed in the fetoplacental circulation. It is not clear at present whether changes in umbilical vascular resistance directly cause changes in the waveform or if a factor common to both, such as increasing vascularization during gestation, causes the decreases in both umbilical vascular resistance and S/D ratio. Morrow et al.[5] were able to dramatically increase S/D ratio in sheep fetuses by embolization with polyethylene microspheres injected into the lower aorta every 30 minutes. Over this short period of time umbilical vascular resistance and S/D ratio were highly correlated. On the other hand, Trudinger et al.[6] observed that a significant change in S/D ratio occurred after only 4 days of daily embolization of the umbilical vascular bed, whereas a change in its vascular resistance was not observable until 9 days of embolization. Therefore, at this time the relationship between S/D ratio and umbilical vascular resistance is not clear. For this reason we have infused vasoactive agents into the fetal hind limb vein while measuring fetal arterial pressure and umbilical blood flow to determine whether the relationship between S/D ratio and umbilical vascular resistance is maintained during acute increases in umbilical vascular resistance.

In the present investigation acute increases in um-

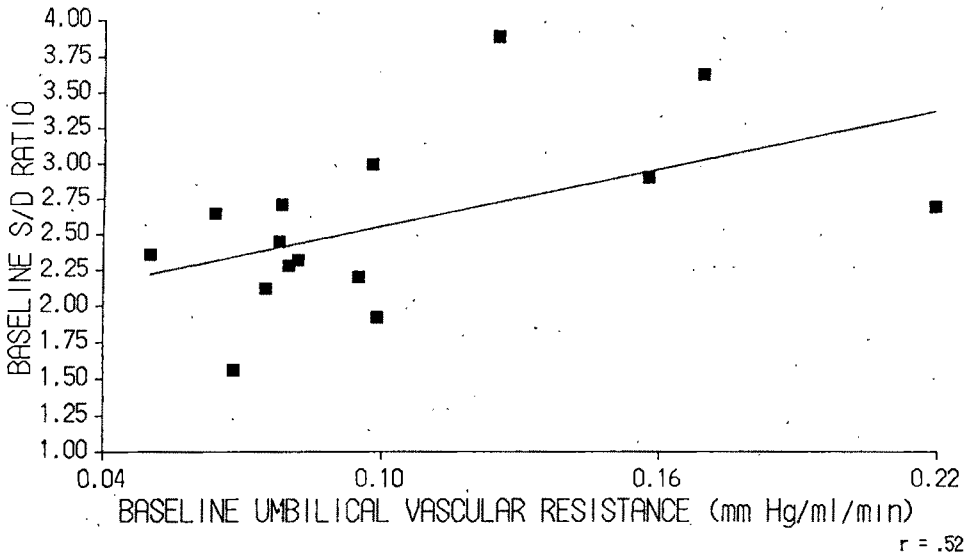


Fig. 4. Relationship between baseline S/D ratio and baseline umbilical vascular resistance before infusion of vasoactive substances. S/D ratio was significantly related to umbilical vascular resistance ($r = 0.52$, $n = 15$, $p < 0.05$). Line is least squares fit of data.

bilical vascular resistance were not accompanied by the predicted change in S/D ratio. All five vasoactive agents produced significant dose-related increases in umbilical vascular resistance, but did not significantly increase the magnitude of the S/D ratio. On the contrary, S/D ratio decreased during infusion of angiotensin II, arginine vasopressin, norepinephrine, and serotonin. Although S/D ratio was significantly related to umbilical vascular resistance before infusion of vasoactive substances, this relationship was not maintained, for the most part, during infusion of these substances, and in the case of norepinephrine, the opposite result occurred; an increase in umbilical vascular resistance was accompanied by a decrease in S/D ratio. The relationship between S/D ratio and umbilical vascular resistance was only maintained during infusion of the thromboxane A_2 sympathomimetic agent U-46619. As umbilical vascular resistance increased during infusion of U-46619, S/D ratio increased.

The reason for the different S/D ratio responses to the different vasoactive agents cannot be determined from this investigation. One possible explanation is that these agents act on different segments of the fetoplacental vascular bed. S/D ratio is related to the number of small arterioles available for blood flow in the fetoplacental vascular bed.[3, 4] In response to the decrease in fetoplacental blood flow caused by infusion of vasoconstrictors smaller arterioles downstream of constricted arterial vessels may dilate. This vasodilation could then result in sufficient microvascular pressure to maintain flow of blood through microvessels or perhaps initiate flow in microvessels that did not have flow previously, thereby maintaining or decreasing S/D ratio despite a decrease in total umbilical blood flow. The thromboxane A_2 sympathomimetic agent U-46619 may produce a more widespread vasoconstriction throughout the fetoplacental vascular bed, resulting in more vessels without flow and an increased S/D ratio.

Other factors that may influence S/D ratio include changes in cardiac output and heart rate. Infusion of these vasoactive substances are likely to alter fetal cardiac output and may thereby alter S/D ratio. However, the effects of each vasoactive substance on cardiac output and S/D ratio are difficult to predict. The effect of heart rate is more straightforward. It has been shown previously[10, 11] and again in this investigation that heart rate and S/D ratio are inversely related. As heart rate decreases there is more time for diastolic flow to decrease, resulting in an increased S/D ratio. Conversely, S/D ratio decreases with increasing heart rate.

In the present investigation, changes in heart rate alone cannot explain the changes observed in S/D ratio during infusion of vasoactive substances. During infusion of angiotensin II and arginine vasopressin, no relationships between S/D ratio and either heart rate or umbilical vascular resistance could be shown. Because heart rate decreased and umbilical vascular resistance increased, an increase in S/D ratio would be predicted during infusion of angiotensin II or arginine vasopressin. Instead, S/D ratio decreased with increasing doses of these two agents. During infusion of norepinephrine and serotonin umbilical vascular resistance and heart rate both increased. The relationships between S/D ratio and heart rate and between S/D ratio and umbilical vascular resistance were of borderline statistical significance during norepinephrine infusion.

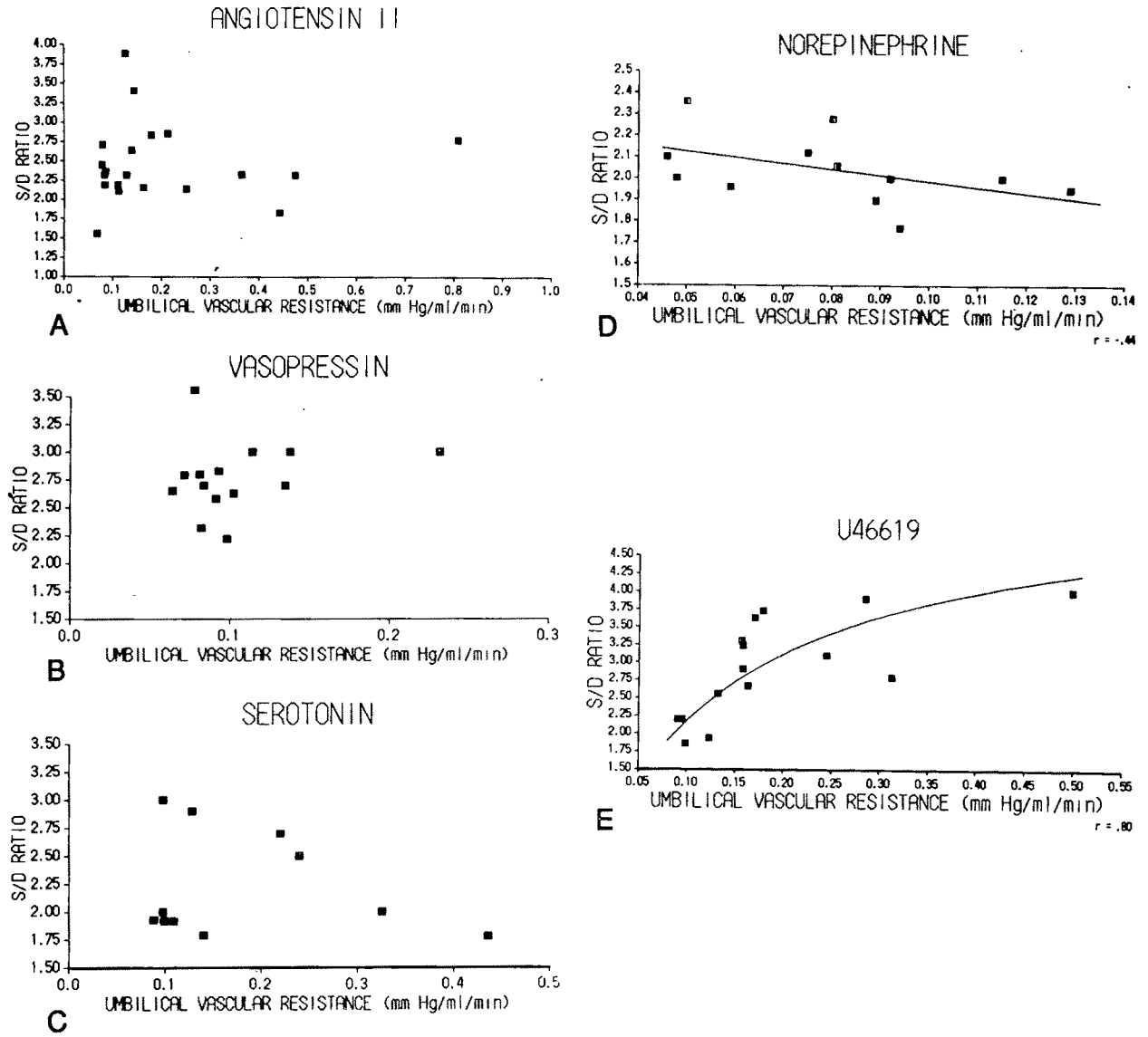


Fig. 5. Relationships between S/D ratio and umbilical vascular resistance during infusion of each of five pressors. **A,** angiotensin II (n = 4 sheep · 4 doses + baseline). **B,** arginine vasopressin (n = 2 sheep · 6 doses + baseline). **C,** serotonin (n = 3 sheep · 3 doses + baseline). **D,** norepinephrine (n = 3 sheep · 3 doses + baseline). Line is least squares fit. **E,** U46619 (n = 3 sheep · 4 doses + baseline). Line is least squares curvilinear fit of S/D ratio^{-1} versus vascular resistance^{-1}. Only the increase in S/D ratio with increasing umbilical vascular resistance during infusion of U-46619 reached statistical significance ($p < 0.01$). S/D ratio appeared to decrease with increasing umbilical vascular resistance during infusion of norepinephrine ($p < 0.10$).

S/D ratio decreased with increasing heart rate as predicted, but decreased with increasing umbilical vascular resistance during norepinephrine infusion. No significant relationships between S/D ratio and either heart rate or umbilical vascular resistance could be observed during serotonin infusion, although S/D ratio decreased with increasing doses of serotonin. In an effort to differentiate between heart rate effects and umbilical vascular resistance effects on S/D ratio, data were analyzed with the use of multiple linear regression. No additive effects of heart rate and umbilical vascular resistance could be shown. S/D ratio changed in the direction expected if umbilical vascular resistance determines S/D ratio only during infusion of U-46619, although the increase in S/D ratio might also be a result of decreasing heart rate with increasing dose of U-46619.

These results support our previous conclusion[1] that the clinical usefulness of waveform analysis may lie more in its ability to detect abnormalities in the size or

function of the fetoplacental vascular bed, rather than strictly changes in umbilical blood flow. Although the magnitude of S/D ratio is related to umbilical vascular resistance under normal conditions, this relationship can disappear during acute changes in umbilical vascular resistance. Under these conditions, S/D ratio is no longer an adequate predictor of umbilical blood flow.

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Role of the endothelium in adrenergic responses of mesenteric artery rings of pregnant rats

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Responses to adrenergic agents were measured on rings of mesenteric artery of nonpregnant and pregnant rats at 21 days' gestation. In tissues from pregnant rats, norepinephrine, and phenylephrine were less sensitive than in rings from nonpregnant animals; maximum responses were not affected. The effect of isoproterenol was not modified in tissues from pregnant rats. The presence of endothelium in tissue rings was evaluated as fractional relaxation to acetylcholine. Sensitivity to phenylephrine and norepinephrine was inversely related to the effect of acetylcholine. This relationship was similar in slope in both groups but different in intercept. The sensitivity to isoproterenol was directly related to the presence of endothelium (curves similar in both slope and intercept). This demonstrates that the responses of mesenteric artery rings depends on the presence of endothelium. Furthermore, vascular endothelium is not involved in the blunted responses to adrenergic vasoconstrictor during pregnancy. (AM J OBSTET GYNECOL 1990;163:229-34.)

Key words: Endothelium, mesenteric artery, adrenergic agents, pregnancy

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Blood pressure decreases in pregnant rats approaching parturition.[1,2] At the same time the vasculature becomes less sensitive to vasoconstrictor agents such as angiotensin II, arginine-vasopressin, and norepinephrine.[1,3-5] Similarly, the in vitro response to vasoconstrictors is also decreased in isolated vascular tissues from different vascular beds.[6-9]

To explain these phenomena, several studies exam-

ined the role of vasodilating prostaglandins in the regulation of blood pressure and vascular reactivity during pregnancy.[10-12] Indeed, pregnancy was found to be associated with increased uterine release, plasma levels, and urinary excretion of prostaglandins in rats and rabbits.[13-15] The endothelium of blood vessels releases significant quantities of prostaglandins and of endothelium-derived relaxing factor, recently identified as nitric oxide.[16-18] The responses to many vasoconstrictor agents are blunted in the presence of endothelium in isolated vascular tissues.[19-23]

To verify whether the blunted responses to vasoconstrictors in term pregnancy are related to the presence of endothelium, we measured the reactivity of the superior mesenteric artery to vasoconstrictor and vasodilator adrenergic agents. The fractional relaxation of phenylephrine-precontracted vessels by acetylcholine was also measured to ascertain the functional status of endothelium. Although the effects of pregnancy or of vascular endothelium on the responsiveness of blood vessels have been well documented for vasoconstrictor agents, their effects on the action of vasodilator agents have not been studied. Furthermore, the concurrent effects of both pregnancy and the presence of vascular endothelium on the responsiveness of vessels to vasoactive agents have never been studied. These are the subjects of this article.

Methods

Ten-week-old female Sprague-Dawley rats obtained from Charles River Canada (St-Constant, Quebec, Canada) were mated with males of the same age. The morning on which vaginal smears were found to contain spermatozoa was labeled day 1 of gestation. The experiments were performed on the twenty-first day of pregnancy (i.e., when the animals reached 13 to 14 weeks of age); unmated age-matched females served as controls. Rats were decapitated, and the superior mesenteric artery was rapidly removed and placed in cold Krebs solution. The artery was cut transversely to obtain two rings 5 mm long. Small hooks made with 30-gauge needles were carefully inserted into the rings to vertically suspend them in 15 ml glass-jacketed organ baths. The tissues were connected to isometric force-displacement transducers (FT-03, Grass Instrument, Quincy, Mass.) connected to a Grass polygraph #7. They were stretched to a passive tension of 1.0 gm, which in preliminary experiments (Parent A, St-Louis J. Unpublished data) was found to be the optimum one for mesenteric rings of both pregnant and nonpregnant rats. The tissues were then equilibrated for 1 hour in Krebs solution while their passive tension was regularly adjusted. The Krebs solution used in these experiments contained the following compounds: sodium chloride, 118 mmol/L; sodium bicarbonate, 25 mmol/L; potassium chloride, 4.7 mmol/L; calcium chloride, 2.5 mmol/L; magnesium sulfate, 1.18 mmol/L; potassium phosphate, 1.18 mmol/L; and dextrose, 5.5 mmol/L. The pH was 7.4 at 37° C, and the solution was bubbled with a mixture of 95% oxygen and 5% carbon dioxide.

After equilibration, phenylephrine (10^{-6} mol/L) was added to the bathing solution to measure tissue reactivity. At the plateau phase of this response to phenylephrine, the functional integrity of the endothelium was assessed by application of acetylcholine (10^{-4} mol/L; in preliminary experiments it was observed that this concentration of acetylcholine produced a maximal relaxation in all tissues tested when precontracted with this high concentration of phenylephrine (10^{-6} mol/L, ≈ concentration producing 50% of the maximum response or EC_{50}). This response was measured as the fractional relaxation of phenylephrine-induced contraction (i.e., relaxation in centimeters divided by the plateau response to phenylephrine in centimeters). Cumulative concentration-response curves to norepinephrine, phenylephrine, and isoproterenol were subsequently evaluated for each tissue. Concentration-response curves were measured in this sequence in all experiments. The concentration-response curve of isoproterenol was measured after the tissue had been precontracted with 3×10^{-7} mol/L phenylephrine.

Data analysis. Each experimental concentration-response curve was analyzed by microcomputer with the ALLFIT program[24] to determine the concentration producing 50% of the maximum response (EC_{50}) and the maximum asymptote of the response. Statistical comparisons were made by Student's *t* test on the mean pD_2 values (negative logarithm of EC_{50}) and mean asymptote of the individually fitted curves. Linear regression was used to measure the relationship between sensitivity of the agent (pD_2) and the functional integrity of the endothelium (fractional response to acetylcholine). Statistical differences for slope and intercept were evaluated by covariance analysis.

Agents used. The agents used in these studies, (−)-arterenol hydrochloride (norepinephrine), (−)-phenylephrine hydrochloride (phenylephrine), (±)-isoproterenol hydrochloride (isoproterenol), and acetylcholine chloride (acetylcholine) were purchased from Sigma Chemical Co. (St. Louis).

Results

The contractile response to 10^{-6} mol/L phenylephrine was similar in the two groups of mesenteric artery rings obtained from nonpregnant and pregnant rats (0.65 ± 0.09 and 0.64 ± 0.06 gm, respectively; $n = 18$ in each group). The relaxation induced by 10^{-4} mol/L acetylcholine at the plateau response to phenylephrine varied from zero to full relaxation; the mean fractional

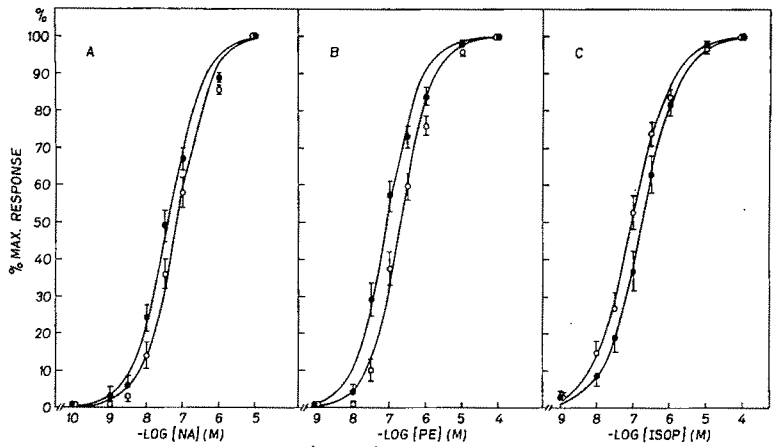


Fig. 1. Concentration-response curves to norepinephrine *(NA)*, phenylephrine *(PE)*, and isoproterenol *(ISOP)* on superior mesenteric artery rings of nonpregnant *(closed circles)* and term pregnant *(open circles)* rats. The contractile responses to norepinephrine and phenylephrine (panels **A** and **B**) are expressed in percent maximum response recorded as tension in grams. In panel *C* the vasorelaxant response to isoproterenol was measured on tissues precontracted with PE/3 × 10^{-7} mol/L) and tissue relaxation is also expressed as percent maximum response. (*Abscissa*, Negative log of agonist concentration in moles per liter. $N = 18$ for each curve.)

Table I. Sensitivity and responsiveness of the mesenteric artery rings to norepinephrine, phenylephrine, and isoproterenol in nonpregnant and 21-day pregnant rats

	Norepinephrine		*Phenylephrine*		*Isoproterenol*	
Group	*pD_2 (EC_{50} in mol/L)*	*Maximum response (gm)*	*pD_2 (EC_{50} in mol/L)*	*Maximum response (gm)*	*pD_2 (EC_{50} in mol/L)*	*Maximum response (gm)*
Nonpregnant ($n = 18$)	7.44 ± 0.08 (3.6×10^{-8})	1.00 ± 0.09	7.09 ± 0.09 (8.2×10^{-8})	1.01 ± 0.09	6.83 ± 0.10 (1.5×10^{-7})	0.84 ± 0.07
Pregnant ($n = 18$)	7.20 ± 0.10 (6.3×10^{-8})	1.17 ± 0.11	6.72 ± 0.08 (1.9×10^{-7})	1.13 ± 0.11	7.07 ± 0.09 (8.5×10^{-8})	0.77 ± 0.09
	$p = 0.05$	NS	$p < 0.005$	NS	$0.05 < p < 0.10$	NS

relaxation of rings from nonpregnant and pregnant animals was 0.36 ± 0.08 and 0.39 ± 0.09, respectively.

Fig. 1 depicts the concentration-response curves of norepinephrine, phenylephrine, and isoproterenol in mesenteric artery rings of nonpregnant and pregnant rats. Gestation shifted the concentration-response curves of norepinephrine and phenylephrine to the right, indicating a reduction in sensitivity to both agents. In fact, Table I shows that the EC_{50} to both agents doubled in pregnancy, whereas the maximum responses were not affected. The vasorelaxant concentration-response curve of isoproterenol on phenylephrine-precontracted mesenteric artery rings was shifted to the left in tissues from pregnant rats (Fig. 1, *C*), suggesting an increase in sensitivity. This was not confirmed by statistical analysis of the data in Table I, where the enhanced sensitivity to isoproterenol is at the limit of significance, whereas the maximum response is statistically identical in both groups of rings. It should be noted that the responses to 3 × 10^{-7} mol/L phenylephrine to precontract the vessels to obtain concentration-response curve to isoproterenol were statistically similar (0.80 ± 0.07 and 0.72 ± 0.09 gm for tissues from nonpregnant and pregnant rats, respectively).

When the raw data were carefully studied, it was observed that the fractional relaxation induced by acetylcholine had some kind of relationship with sensitivity of these vasoactive agents; hence we performed analysis of covariance on regression lines of the pD_2 for each vasoactive agent with fractional relaxation by acetylcholine as an indicator of the functional presence of the endothelium on the luminal surface of the vessels. The results of this analysis are reported inFig. 2 and Table II. For the three agents, especially for norepinephrine and phenylephrine, it can be seen that the relationship between pD_2 and the fractional response to acetylcholine was highly significant (correlation coefficient Table II) in both control and pregnant rats. When the curves are analyzed with covariance analysis

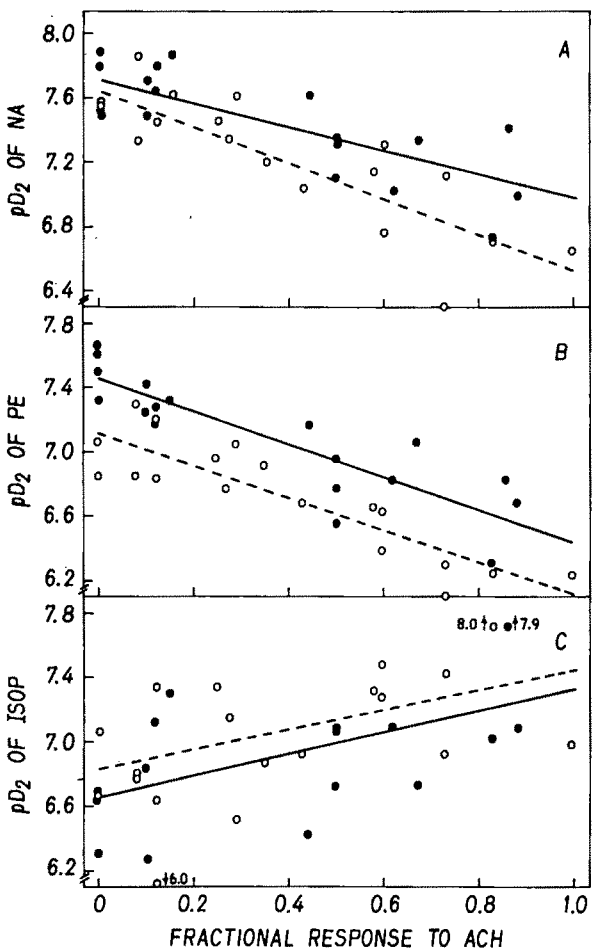


Fig. 2. Linear regression of the sensitivity of superior mesenteric artery rings to norepinephrine *(NA)*, phenylephrine *(PE)*, and isoproterenol *(ISOP)* versus the fractional response of the vessels to acetylcholine (10^{-4} mol/L). Tissues were the same as used in Fig. 1 and were obtained from nonpregnant *(closed circles–solid line)* and term pregnant *(open circles–broken line)* rats. *(Ordinate,* Sensitivity to the agonist as measured by the pD_2 in each tissue. *Abscissa,* Fractional response to acetylcholine [10^{-4} mol/L] on phenylephrine [10^{-6} mol/L]–precontracted vessels.)

(Table II), it is evident that with the three agents the slope of the curves was not different between tissues from pregnant and nonpregnant rats, whereas their elevation was significantly different for the vasoconstrictors but not for isoproterenol. These data, especially the slope, indicate that sensitivity to the vasoconstrictors (norepinephrine and phenylephrine) was decreased by one unit of pD_2 when comparing tissues in which the endothelium was functionally absent with those in which it was functionally intact. For isoproterenol, the increase in sensitivity of pregnant rats was not significant (Fig. 1) nor was the elevation of the curve of the effect of the presence of endothelium on pD_2 (Fig. 2, *C*). This indicates that the measured sensitivity to vasoconstrictor agents, like norepinephrine and phenylephrine, and to vasodilators, like isoproterenol, depends on the functional presence of the endothelium and that this phenomenon is identical for control and pregnant rats. The data also suggest that the decreased sensitivity to vasoconstrictor agents in pregnant rats is independent of the presence of the endothelium.

Comment

The endothelium of blood vessels has numerous important functions, including the induced secretion of substances that affect blood fluidity (e.g., prostaglandins) and vascular tonus (e.g., endothelium-derived relaxing factor).[18] During pregnancy circulating blood decreases in osmolality[25] and vascular resistance is reduced.[26] Because pregnancy is associated with diminished vascular sensitivity to vasoconstrictor agents, we conducted these experiments to evaluate the possible involvement of the endothelium of blood vessels in this lower vascular resistance.

We observed that the sensitivity of the superior mesenteric artery to the three vasoactive agents used (norepinephrine, phenylephrine, and isoproterenol) was dependent on the functional presence of the endothelium in tissue rings. Indeed, sensitivity to both norepinephrine and phenylephrine was decreased tenfold (1 log unit as shown by the slope of the curves in Table II) when the endothelium was functionally intact (total reversal of 10^{-6} mol/L phenylephrine precontraction by 10^{-4} mol/L acetylcholine). It should be noted that the maximum responses to both phenylephrine and norepinephrine were not affected by the functional presence of the endothelium. The increased sensitivity to the vasorelaxant effect of isoproterenol was less markedly influenced by the presence of the endothelium (+0.72 log unit of difference in sensitivity between absent and full responses to acetylcholine). This effect of the endothelium on the sensitivity to vasoactive adrenergic agents was not modified by incubating the tissues in medium containing 10^{-5} mol/L indomethacin (data not shown), indicating that the vasorelaxant influence of the endothelium was not the result of cyclooxygenase activity (e.g., prostaglandin-like).

Decreased sensitivity to vasoconstrictor agents during pregnancy has been observed both in vivo and in vitro.[1, 3, 5, 6, 8, 9] Our results confirm these observations and furthermore show that the presence of the endothelium, although it greatly affects the sensitivity to vasoactive agents, is not responsible for the decreased response to vasoconstrictors during pregnancy. This would have occurred if the endothelium-dependent relaxation of blood vessels had been facilitated during pregnancy, but our data do not support such a role for the endothelium in the decreased sensitivity to vasoconstrictors in this condition. Such a phenomenon was recently noted in spontaneously diabetic rats with a

Table II. Linear relationships of the pD_2 of norepinephrine, phenylephrine, and isoproterenol to the fractional response to acetylchloine in mesenteric artery ring

	NE			*PE*			*ISOP*		
Group	*Slope*	*Intercept*	*r*	*Slope*	*Intercept*	*r*	*Slope*	*Intercept*	*r*
Nonpregnant ($n = 18$)	−0.80	7.72	0.79 $p < 0.001$*	−1.01	7.44	0.87 $p < 0.001$	0.76	6.56	0.55 $p < 0.025$
Pregnant ($n = 18$)	−1.10	7.65	0.86 $p < 0.001$	−1.00	7.11	0.88 $p < 0.001$	0.62	6.83	0.52 $p < 0.05$
Covariance analysis	NS	$p < 0.025$†		NS	$p < 0.001$		NS	$0.05 < p < 0.10$	

*Significance of r was evaluated by Student's t test.

†Covariance analysis predicts differences in elevation of the regression lines instead of in exact differences between intercepts.

functional impairment of endothelial-dependent relaxation of blood vessels.[27] Our current finding is supported by the results in Fig. 2 and Table II. In fact, the identical slopes but different intercepts for the curves shown in Fig. 2 indicate that the sensitivity (slope) of endothelium-derived relaxing factor liberation by the endothelium is identical in tissues from nonpregnant and pregnant rats but that the intrinsic sensitivity of vessels to these agents (intercept) is different in the two sets of tissues. This suggests that the decreased sensitivity of blood vessels to vasoactive agents during pregnancy is linked to their overall reactivity without any involvement of the endothelium. Our study does not, however, discriminate whether the decreased reactivity is the consequence of functional modification of smooth muscle cells or of mechanical properties of the blood vessel wall, as previously suggested.[28, 29] Furthermore, the action of isoproterenol, shown to be increased in the presence of endothelium, is not modified in sensitivity during pregnancy, confirming earlier observations from our laboratory that the effect of vasodepressor agents (atrial natriuretic factor[30]; bradykinin, and sodium nitroprusside[31]) are not affected at the end of gestation in the rat.

The results of our experiments confirm the findings of Teeuw and De Jong[1] that the vasodepressor action of acetylcholine is identical in nonpregnant and term pregnant rats, whereas the responses to vasoconstrictor agents are markedly decreased in the latter. This unmodified vascular action of acetylcholine in pregnancy, reported long before the original observation of Furchgott and Zawadsky[16] on the influence of endothelium on vascular tissues, is confirmed and explained in our studies. Indeed, the mean response to acetylcholine (10^{-4} mol/L) on phenylephrine (10^{-6} mol/L–precontracted vessels was identical in tissues of nonpregnant and term pregnant rats (fractional relaxation was 0.36 ± 0.08 and 0.39 ± 0.03, respectively; difference not significant.).

Recently Yanagisawa et al.[32] identified and characterized endothelin, a potent vasoconstrictor peptide from the supernatant of cultured porcine aortic endothelial cells. This peptide, if present in the endothelium of blood vessels of the rat, does not appear to play a role in our results since the changes in sensitivity observed in these experiments with the presence of a functional endothelium were always compatible with the involvement of a relaxing factor.

It was reported that vascular endothelium is actively involved in the metabolism of norepinephrine.[33, 34] This issue was not investigated in our study, but if the results of Fig. 2 are considered, it can be expected that with phenylephrine (panel *B*) and with isoproterenol (panel *C*), this activity, if involved, was not modified during pregnancy. With norepinephrine (panel *A*) there was some change in the slope of regression line linking sensitivity and functionality of the endothelium, but this did not reach statistical significance. If this difference were to occur, the vascular endothelium of pregnant rats would be expected to metabolize norepinephrine more effectively (higher slope); this remains to be investigated.

In conclusion, our series of experiments indicates that sensitivity to vasoactive adrenergic agents is dependent on the presence of the endothelium in the mesenteric artery. This anatomic structure is not responsible, however, for the decrease sensitivity of blood vessels to vasoconstrictor agents at the end of gestation in the rat.

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HBcAg identification in the placental cytotypes of symptom-free HBsAg-carrier mothers: A study with the immunoperoxidase method

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In this study the presence of HBcAg in placental tissue of symptom-free HBsAg-carrier mothers has been determined by the immunoperoxidase technique. The presence of HBcAg in the major placental cytotypes was mostly limited to the trophoblastic lineage. Moreover the activated macrophages with their strong cytoplasmic reaction to the antigen phagocytosis play a remarkable role in the immune response. Because there are continuous channels that link the human amnion through the trophoblastic lineage, including the endovascular trophoblast with maternal decidual vessels, a functional exchange system may be considered valid. This would influence the transmission of infection. (Am J Obstet Gynecol 1990;163: 235-9.)

Key words: HBcAg, immunoperoxidase, trophoblast

During its developing phases the infiltrating trophoblast forms bridges between the tips of the anchoring villi and maternal decidua and invades deep into the lumen of uterine spiral arteries,[1] getting in direct contact with the maternal infected blood. The obstetric anamnesis of HBsAg-carrier mothers, characterized by otherwise unexplained intrauterine deaths, fetal distress, or preterm deliveries, could be explained by placental functional alteration. This has been proved by the histologic evidence acquired when examining specimens. The placentas showed a remarkable congestion in the chorionic villi of the vessels with possible interruption of the walls that communicate with each other. Stroma edema was evident. In this study we have tried to define both the seriousness and the nature of viral

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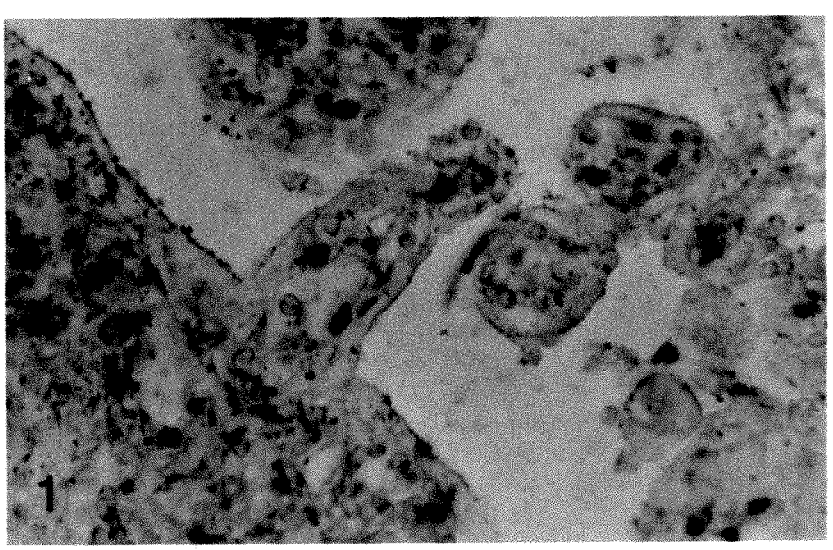


Fig. 1. Strong positive reaction to HBcAg in the villi.

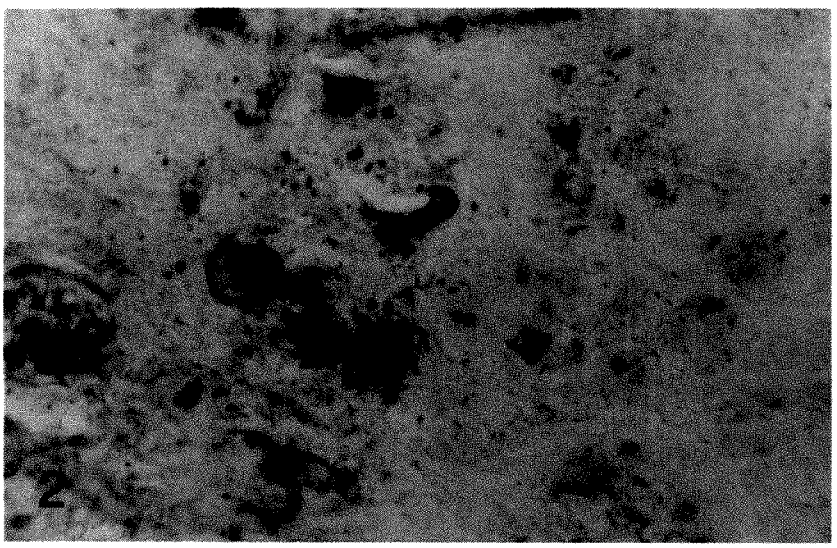


Fig. 2. Large decidual reactive cells.



Fig. 3. Clumps of small decidual cells involved in the antigen presentation.

injury in placental tissue of symptom-free HBsAg-carrier methods.

Material and methods

Sections of placentas were obtained from nine women with pregnancies at term; of these, two underwent cesarean section (Table I). All specimens were fixed and embedded in paraffin. The immunoperoxidase technique against HBcAg was carried out with 3,3′-diaminobenzidine and aminoethyl carbazole (Dako Pat kit system, Dako Corp., Santa Barbara, Calif.) on 5 μm sections. Positive and negative controls were also effected. After counterstaining with 0.2% aurum chloride, the sections were mounted in glycerol–phosphate-buffered saline solution.

Results

The HBcAg presence was demonstrated in all placentas of HBsAg-carrier mothers. In the chorionic tissue the endothelia of fetal vessels, fibroblasts, Hofbauer cells, and trophoblastic columns of the septa showed a strong positivity (Fig. 1). The same occurred in the decidua, where the cells of the infiltrating trophoblast, comprising multinuclear cells[2] and large and small cells,[3] were strongly reactive.

The large decidual cells were sometimes surrounded

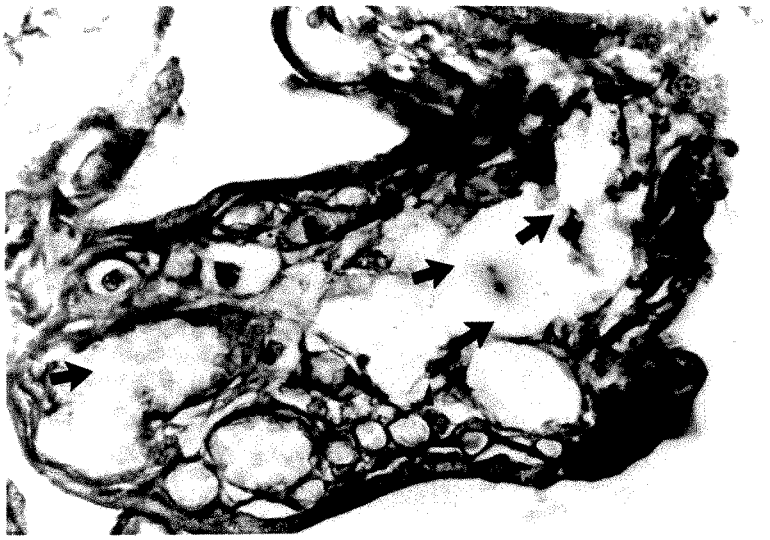


Fig. 4. Damage of endothelial fetal vessels.

Table I. HBsAg symptom-free carrier mothers (nine cases)

Case No.	Parity	Course of pregnancy		Delivery	Gestational age (wk)	Placental indexes			Neonates	
		First trimester	Third trimester			Weight (gm)	Diameter (cm)	Thickness (cm)	Apgar score	Weight (gm)
1	1-0-0-1	Threatened abortion	Threatened premature labor	Spontaneous	38	400	16 × 18	3	2-3-7	2300
2	2-1-1-2*	Threatened abortion	Threatened premature labor	Spontaneous	40	500	19 × 20	3.5	9-10	3600
3†	0-0-0-0	Threatened abortion	Echography, uterus small for date	Cesarean, fetal distress	40	450	18 × 20	3	8-9	2700
4	0-0-0-2	Physiologic	Threatened premature labor	Cesarean, 2 previous cesarean sections	40	400	16 × 19	2.5	9-10	3700
5	0-0-0-0	Physiologic	Physiologic	Cesarean, uterine inactivity	40	650	20 × 22	3.5	10	3000
6	0-0-0-0	High GOT and GPT during pregnancy	Hospitalization at 30 wk, threatened premature labor, hepatogestosis	Medical induction at 42 wk, cesarean, uterine inactivity	42	550	18 × 21	3	10	2850
7	4-0-2-3	Physiologic	Physiologic	Cesarean, fetal distress	39	570	19 × 21	3	1-7-9	2850
8	0-0-0-0	Physiologic	EPH gestosis, echography, uterus small for date	Cesarean, EPH gestosis, fetal distress	38	570	18 × 21	3	9-9	2900
9‡	0-0-0-0	Physiologic	Threatened premature labor, premature rupture of membranes	Cesarean, uterine inactivity, initial fetal distress	40	650	20 × 23	3.5	6-7	3750

GOT, Glutamic oxaloacetic transaminase; *GPT*, glutamic pyruvic transaminase; *EPH*, edema-proteinuria-hypertension.
*Obstetric anamnesis (baby died 8 days after birth); two babies with connatal hepatitis; abortion after 24 weeks of gestation.
†Baby was stillborn.
‡Father affected by hepatic cirrhosis.

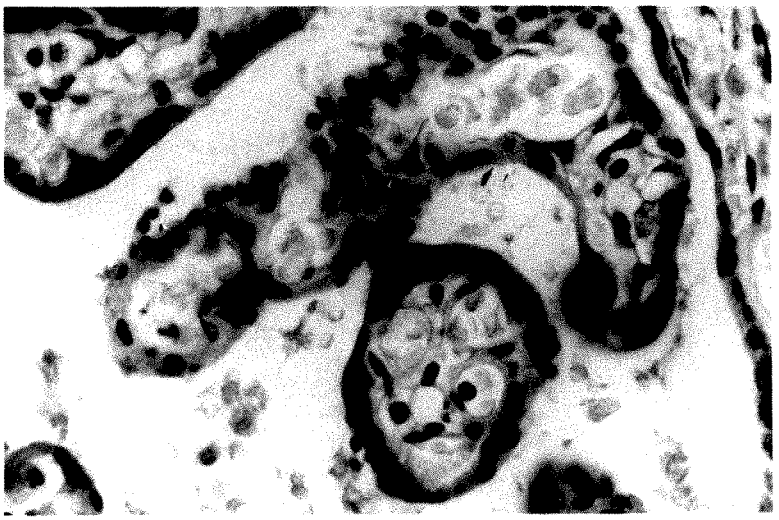


Fig. 5. Villous stromal edema and vessel congestion.

by a positive border or had a uniform cytoplasmic reactivity. Moreover they often showed a strong nuclear staining (Fig. 2). Clumps of small cells, with very strong reactive cytoplasm, stand out clearly against the negative background of decidual tissue (Fig. 3).

At routine staining by emetoxylin-eosin there appeared a stromal edema and remarkable vasal congestion that sometimes culminates in destruction of fetal-placental blood vessels (Figs. 4 and 5). The congestion appeared related to a probable HBcAg vasculotropic force, because it would act as direct mediator of endothelial cell injury. On the other side the fibrin deposit induced a vascular permeability increase, implicated in the development of tissue edema.[4]

The HBcAg presence was not demonstrated in the endothelium of maternal vessels.

Comment

The condition of HBsAG symptom-free carrier mothers presupposes the activation of immune processes able to confine the viral potentiality within reduced limits, insufficient to cause a manifest illness. At implantation in the uterus the extravillous trophoblasts form anchoring bridges with the maternal tissues, in particular some cells called "endovascular trophoblasts," infiltrate the spiral arteries, and proliferate in vessel lumina.[5] Thus viral injury can operate directly because hepatitis B infection occurs through blood.

Studies carried out with monoclonal antibodies show exactly where trophoblasts are distributed in the placental tissues and the extravillous sites, thus allowing one to distinguish the large, small, and multinuclear trophoblastic cells from those of maternal origin.[2, 3]

If we compare these data with our results it becomes evident that the whole trohpoblastic lineage reacts electively against HBcAg, because it is easily recognized by the strong reactivity assumed by the cytotrophoblastic columns.

The immunoperoxidase staining of the Hofbauer cells and fibroblasts reveals that macrophages are involved as well. Even the small decidual cells, closely associated with lymphocytes in the suppression of the maternal immune response to implantation, are reactive to HBcAg. Moreover, because of their morphologic and histochemical features, they appear as macrophage-like cells. This could suggest that they are Hofbauer cells migrating from the chorionic villi.[3]

In one case of acute hepatitis B the mother was seropositive for HBsAg in the seventh and eighth months but negative in the ninth month, and the baby was born seropositive. This leads us to believe that the last trimester is the most likely time for transplacental spread.[6] Taking into account that recent studies have shown the existence of a selective mechanism of transfer between the amniotic and maternal compartments, we may conclude that placentas play a primary role in transferring the maternal infection to the fetus. However, the viral injury can be very weak and not result in a neonatal disease, especially if the virosis is not aggressive and specific maternal immunoglobulins are present, thus influencing the course of the infection.

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LETTERS TO THE EDITORS

Editors' note: Readers may note we are publishing more Letters to the Editors in an effort to reduce the backlog and improve the publication time.

Maternal serum α-fetoprotein level useful screening test

To the Editors: The question of Dr. J. D. Stephens (Unexplained elevated maternal serum α-fetoprotein level associated with third-trimester problems [Letter]. AM J OBSTET GYNECOL 1989;161:500) was addressed by different investigators several years ago.

In the more recent study of Walters et al.[1] unexplained elevated maternal serum α-fetoprotein was found to be associated with a higher incidence of previous second-trimester and recurrent abortions as well as preterm delivery, low birth weight, and proteinuric preeclmapsia (both superimposed and de novo), the last complication being first reported by Moore and Redman.[2] Walters et al. found that the incidence of proteinuric preeclampsia was 12.5% in the study group versus 0% in the control group, and accounted for 47% of the babies with low birth weights in the study group. Maternal serum α-fetoprotein level may become the most useful screening test for high-risk pregnancies.

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Clindamycin dosage scheduling for acute pelvic infection

To the Editors: Clindamycin phosphate continues to be a widely used antibiotic for the infections of the female genital tract. Recent studies have indicated that administration of clindamycin 600 mg every 8 hours combined with gentamycin or tobramycin is effective in curing presumed infections of intraabdominal origin in 84%[1] to 95%[2] of the patients. *Bacteroides fragilis* is extremely sensitive to clindamycin and minimal inhibitory concentration averages <1.00 μg/ml. The reported minimal inhibitory concentration after the fourth dose of intravenous clindamycin is 1.7 μg/ml[4] and this should provide enough concentration to cover the presumed infections with *Bacteroides fragilis*.

The infectious diseases departments in many institutions recommend that the standard dose of injectable clindamycin need not be higher than 600 mg every 8 hours. Since this policy was adopted at our institution we did a retrospective study to determine whether there was any difference in the clinical response of the patients admitted for pelvic inflammatory disease to clindamycin 900 mg every 8 hours to clindamycin 600 mg every 8 hours. Forty-five patients were selected randomly from each group and their findings are presented in Table I. Both groups of patients received gentamycin or tobramycin.

Table I. Average number of days for response

	White cells	*Temperature*	*Abdominal pain*
Clindamycin 900 mg every 8 hr	3	2.8	3.0
Clindamycin 600 mg every 6 hr	4	2.8	3.2
p Value	—	—	NS

The results indicate that clindamycin 600 mg every 8 hours is equally effective as 900 mg every 8 hours. The regimen of clindamycin 600 mg every 8 hours has resulted in a 30% decrease in cost of antibiotics at our institution. It is hoped that with the previous studies and more prospective studies, the Center for Disease Control recommendations will change to 600 mg clindamycin every 8 hours for presumed pelvic inflammatory disease.

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Magnesium supplementation in pregnancy

To the Editors: It was with great interest that we read the paper of Sibai et al. (Sibai BM, Villar MA, Bray B. Magnesium supplementation during pregnancy: a double-blind randomized controlled clinical trial. AM J OBSTET GYNECOL 1989;161:115-9).

In view of the difference in results between this study and our own[1] it is regrettable that the authors have not adequately outlined some major differences in study design:

Table I. Differences in the results of the Sibai study becoming significant with a 10-fold increased population

	p Value
Birth weight	<0.005
Placental weight	<0.002
Small for dates	<0.05
Apgar score at 5 min < 7	<0.05

1. The study of Sibai et al. compares a low-dose versus a high-dose magnesium supplementation, whereas in our study no magnesium supplementation was compared with a high dose.
2. The study group of Sibai et al. was restricted to young primigravid women to have patients at higher risk of preeclampsia.
3. Furthermore, magnesium supplementation was started at a later state in pregnancy, 17.8 in average versus 13.3 weeks in our study.

If the authors find an extrapolation to a study population 10 times the one used acceptable to rule out statistical significance in the difference of frequency of preterm labor in the two groups, they should have applied the same approach to other parameters and would have found significant differences in favor of the high magnesium group (Table I).

It should be clearly stated that Sibai et al. did not find an effect of elevation of magnesium supplementation from 100 mg to 465 mg daily with intake started after 13 weeks' gestation in young primiparas in the prevention of the development of preeclampsia.

They certainly have not disproved our finding of beneficial effect on overall outcome of early onset high-dose magnesium supplementation in an unselected group when compared with no magnesium supplementation.

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REFERENCE

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Reply

To the Editors: I would like to thank Drs. Spätling and Fallenstein for their interest in our study and for giving me the opportunity to outline some of the problems in their study.[1] It is important to note that we used the same dose of the study drug and the same placebo prepared by the same company that prepared their drugs. In addition, we made sure that all patients received the same prenatal vitamins to ensure similar intake of additional magnesium by both groups. Moreover, we performed serial nutritional recall to assess the amount of magnesium intake from food in both groups. Both of these points are very basic for any nutritional supplementation study. Unfortunately, the above authors did not include these in their study design. I assume that pregnant women in Europe receive prenatal vitamins and that their diet contains some magnesium. Thus, the conclusions of the study by Spätling and Spätling are inappropriate since they did not know the amount of magnesium intake in each group.

Our study included a homogenous group of patients after excluding all associated medical and obstetric complications. Thus, any differences in outcome will definitely be attributed to magnesium effect. In contrast, their study included a heterogenous group of patients with various obstetric complications. As a result, the difference in outcome between the two groups were because of differences in patients studied rather than because of magnesium. It is obvious that all the differences were a result of a higher number of patients with either bleeding or incompetent cervix in the placebo group. I do not believe that magnesium is such a magic drug with the ability to prevent the above complications.

A difference of an average of 4 week's gestation at the time of enrollment between the two studies is meaningless because most women received an average of 22 weeks of magnesium supplementation. In addition, most pregnant women will start prenatal care around this time period.

Finally, I agree with the recent comments of Hibbard that the evidence for dietary supplementation of magnesium in pregnancy is unconvincing.

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Secretion of phospholipases by bacterial pathogens may initiate preterm labor

To the Editors: Evidence for the role of infection in the cause of preterm labor continues to accumulate[1]; however, cause and effect remain to be established. Normal labor at term is associated with an increase in the synthesis of prostaglandins within the uterus.[2] Recently Lopez-Bernal et al.[3] compared prostaglandin E_2 (PGE_2) production by fetal membranes and placenta after preterm labor with that after term labor. The production by amnion and chorion decidua was highest after labor at term, with the lowest rates of production seen after uncomplicated preterm labor. However, amnion and chorion decidua obtained after preterm labor associated with chorioamnionitis produced high levels of PGE_2. The authors concluded that chorioamnionitis causes preterm labor by increasing prostaglandin production in the fetal membranes.

We have previously published in the JOURNAL[4] our finding that common vaginal pathogens release a substance that increases arachidonic acid metabolism when

Table I. Phospholipase A_2 activity in bacterial-conditioned media and ability to stimulate amnion cell arachidonic acid metabolism

Organism	*Phospholipase$_2$ activity (nmol fatty acid hydrolyzed/hr) (mean ± SD)*	*Increase in amnion arachidonic acid metabolism (% of control)*
Streptococcus viridans	11.5 (2.1)	283
Group B streptococcus	10.2 (1.7)	269
Bacteriodes fragilis	6.6 (1.8)	236
Escherichia coli	5.6 (1.9)	202
Lactobacillus acidophilus	0.6 (0.4)	97

added to amnion cells. Both lipoxygenase metabolism to hydroxyeicosatetraenoic acids and cyclooxygenase metabolism to PGE_2 are increased by addition of this substance but the increase in metabolism to PGE_2 predominates. These changes are very similar to those seen in amnion cells obtained after spontaneous labor at term, compared with those obtained at elective cesarean section before labor. We postulated that bacteria may mediate these effects by release of phospholipases.

We have since found that addition of purified phospholipase A_2 to amnion cells results in changes in arachidonic metabolism identical to those caused by addition of bacterial products. We also measured phospholipase activity in the bacterial-conditioned media used in our original experiments with the methods described by Bonney et al.[5] The data shown in Table I revealed that there was a strong positive correlation between the phospholipase activity in any individual bacterial-conditioned medium and the ability of that medium to stimulate overall arachidonic acid metabolism in amnion cell cultures ($r = 0.92$).

Although not definitive proof of cause and effect, the correlation between phospholipase release and stimulation of arachidonic acid metabolism and the similarity between the effects of bacterial products and purified phospholipase A_2 support the hypothesis that common bacterial pathogens release phospholipase, which stimulates prostaglandin production within the fetal membranes. This then may be one mechanism by which preterm labor is initiated.

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Zinc, preeclampsia, and γ-aminobutyric acid

To the Editors: An oversight has occurred in an article of Dr. Lazebnik et al. (Lazebnik N, Kuhnert BR, Kuhnert PM. Zinc, cadmium, and hypertension in parturient women. Am J Obstet Gynecol 1989;161:437-40). The authors state that their finding of lowered placental zinc in preeclampsia "has not been previously reported." We did, in fact, report in 1985 low zinc in placentas of preeclamptic patients,[1] perhaps reflective of generally low tissue zinc including that of brain where it might be relevant to eclampsia.

We continue to believe that low zinc might affect concentrations of brain γ-aminobutyric acid, the inhibitor neurotransmitter, and have some new data. Preliminary results are that plasma γ-aminobutyric acid is lower in preeclamptic patients (93 pmol/ml ± 12 SD) than in normal women in labor (132 pmol/ml ± 38 SD) ($p < 0.05$). There is a drop in plasma γ-aminobutyric acid of 15 pmol/ml in normal women early in labor. Normal nonpregnant women have a plasma γ-aminobutyric acid concentration of 127 pmol/ml (± 17 SD) similar to normal women in labor.

Zinc is involved in maintenance of pyridoxal phosphate concentrations by its activation of pyridoxal kinase[2]; pyridoxal phosphate is a decarboxylation cofactor and deficiency lowers brain γ-aminobutyric acid.[3] The decrease in this inhibitory neurotransmitter would lower the seizure threshold. Significant zinc malnutrition might interfere with transcription of deoxyribonucleic acid to ribonucleic acid[4] and thus production of the protein enzyme pyridoxal kinase.[5] Although plasma pyridoxal phosphate has been found to be insignificantly lower in preeclampsia than in normal pregnancy,[6] "plasma pyridoxal phosphate measurements alone may not accurately reflect either vitamin B_6 nutriture or tissue pyridoxal phosphate levels during pregnancy."[7] Low zinc may be related through pyridoxine metabolism to low γ-aminobutyric acid and seizures.

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Supported in part by a Mental Health Clinical Research Center Grant (MH 41115) to the University of Texas Southwestern Medical Center and R01 MH 37899-03.

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Response declined

Association between autoantibodies and unexplained infertility unproved

To the Editors: Taylor et al.'s recent article (Taylor PV, Campbell JM, Scott JS. Presence of autoantibodies in women with unexplained infertility. AM J OBSTET GYNECOL 1989;161:377-9) claims to show that there is an increased incidence of antibodies to smooth muscle, nuclear components, and phospholipids in women with unexplained infertility. The authors postulate a pathogenic role for these antibodies. Unfortunately, they use a group of pregnant women as their control, which invalidates their conclusion. Use of a group of women with a variety of known causes for their infertility (anovulation, tubal factor, male factor) would be indicated. Taylor's results could be explained in several ways: pregnant women may have a lower level of autoantibodies; alternatively, infertility itself, whether explained or unexplained, could be associated with a higher level of autoantibodies.

Other features of their article need clarification. They state that their infertile group had a laparoscopy that showed "no intrapelvic bar to pregnancy"; what does this mean? Did they have a totally normal pelvis, or were there abnormalities found that were not considered absolute barriers to pregnancy? Neither hysteroscopies nor hysterosalpingograms were performed; were uterine causes of infertility ruled out? Endometrial curettage showed secretory endometrium; was it in phase or were luteal phase defects ruled out by other means?

The association between autoantibodies, especially antiphospholipids, and recurrent pregnancy losses, has been established.[1] An association with endometriosis has been postulated, but further work is needed in this area.[2] I do not believe that Taylor et al.'s study shows an association between autoantibodies and unexplained infertility.

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Reply

To the Editors: In the statement that our infertile group had no intrapelvic bar to pregnancy we meant that laparoscopy showed no evidence of pelvic adhesion nor any sign of endometriosis, with both fallopian tubes being patent to the passage of dye and no evidence of clubbing at the fimbrial end. The endometrial curettage specimens all showed secretory endometrium in phase with the patient's cycle.

Comparison of the group of pregnant women with our group of normal, nonpregnant, age-matched controls (data for the latter not given in the article) shows that a lower level of autoantibodies was not associated with pregnancy per se in our group. Therefore comparison of our infertile group with normal, nonpregnant controls would have confirmed an increased prevalence of autoantibody in these infertile women. However, Dr. Maier's point concerning the control group with explained infertility is entirely valid and emphasizes the need for further work in this area.

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Modified laparoscopy for monitoring transcervical surgery

To the Editors: Use of laparoscopy during transcervical resection of the uterine septum, intrauterine adhesion, and submucous myoma under hysteroscopic control has been reported.[1] To prevent accidental trauma such as uterine perforation or further subsequent intestinal trauma, a laparoscopy was simultaneously used to monitor the transcervical hysteroscopic operation. The procedure was to darken or to turn off the light from the laparoscope while monitoring the light transilluminated from the hysteroscope. If the light from the hysteroscope can be clearly visualized from the laparoscope, it is a dangerous sign that the tip of the hysteroscope is closely approaching the uterine surface. However, because the accuracy of this method greatly depends on the experience of the laparoscopist, even with cautious monitoring, uterine perforation is still encountered. On the other hand, incomplete excision of the intrauterine lesion is experienced because of fear of perforation.

To solve these problems we developed a modified two-step method. The first step involves the conventional monitoring procedures described previously. When the hysteroscope is advanced to a certain point, the second step is performed. The second step is to place the laparoscopic light near the surface of uterus

while darkening or turning off the light from the hysteroscope. By monitoring the light transilluminated from the laparoscope, the operator can not only estimate the thickness of the remaining uterine wall, but also determine the incomplete resected portion.

This modified method enables a homogeneous fundal resection and prevents the risk of uterine perforation and incomplete intrauterine resection.

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Combination therapy has potential complications

To the Editors: I read with interest the case reported by Snyder and Cardwell (Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. AM J OBSTET GYNECOL 1989;161:35-36). I would like to point out a few inaccuracies mentioned in the article.

First, magnesium sulfate is not a calcium channel blocker but a calcium antagonist.

That the authors are not aware of any reports of serious side effects is because they have limited experience with nifedipine[1] and because the combination of nifedipine and magnesium sulfate is seldom used in practice rather than relatively frequently as they state in their article. The potential severity of the complications in combination therapy is highlighted by the occurrence of neuromuscular junction blockade after a homeopathic dose of 500 mg of intravenous magnesium sulfate.

Finally, the use of β-sympathomimetic agents alone for tocolysis is associated with significant maternal[2] and fetal[3] morbidity. The use of combination therapy for tocolysis should be discouraged.[4, 5]

However, I would like to congratulate the authors for publishing this case of drug interaction, which shows how dangerous can be the concomitant use of smooth muscle relaxing agents with different modes of action.[4, 5, 6]

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Reply

To the Editors: We are glad to hear of Dr. Frolich's interest in our recent case report. Perhaps some clarification of the language in the article is needed.

First, calcium antagonists should be used in our report wherever "calcium channel blockers" appears. It may be more accurate to consider magnesium as an ionic antagonist (if it is one at all) and nifedipine as an organic one.[1] We do not pretend that a clear understanding of the mechanism of action of either agent in uterine muscle is known.

The remainder of the comments I think relate to the section of our case report that describes the absence of serious interaction of neuromuscular blockers and calcium antagonists, which are used in combination relatively commonly (as patients with hypertension and angina come to the operating room for anesthetics). We in no way meant to underemphasize the magnitude or gravity of side effects of tocolytics, alone or in combination.

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Heterotopic pregnancy associated with assisted reproductive technology

To the Editors: We read with interest Gamberdella and Marrs' article and its discussion (Gamberdella FR, Marrs RP. Heterotopic pregnancy associated with assisted reproductive technology. AM J OBSTET GYNECOL 1989;160:1520-4) on the incidence and management of heterotopic pregnancy associated with assisted reproduction.

The authors quoted the incidence of heterotopic pregnancies in the literature to be between 1/2600 and 1/30,000 pregnancies. Studies from Israel[1] and Belgium[2] gave an incidence of 1/6778 and 1/4112, respectively.

With the advent of in vitro fertilization–embryo transfer techniques, more patients with tubal damage have conceived with a high incidence of ectopic pregnancy (5% as quoted by Cohen et al.[3]). Consequently,

the incidence of heterotopic pregnancy has increased even further.

Nine cases of heterotopic pregnancies occurred after in vitro fertilization–embryo transfer at Hammersmith Hospital, London, between September 1984 and November 1988. The incidence was 9/312 clinical in vitro fertilization pregnancies (2.9%),[4] which to our knowledge is the largest collected series from one unit.

Gamberdella and Marrs reported the inability of the β-human chorionic gonadotropin level on day 23 after egg collection to delineate the heterotopic pregnancy in their case.

In our experience,[4] earlier levels of serum human chorionic gonadotropin (days 12, 14, and 16 after egg collection) may indicate the presence of multiple gestation. The sonographic appearance of only one intrauterine sac on vaginal ultrasonographic examination should further increase the index of suspicion for heterotopic pregnancy.

We believe that the readers should be aware of this high incidence of heterotopic pregnancy because the diagnosis of this potentially fatal condition could be easily missed.

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Response declined

Plasma atrial arginine vasopressin levels vary little between preeclamptic and control patients

To the Editors: The recent article by Hatjis et al. (Hatjis CG, Greelish JP, Kofinas AD, Stroud A, Hashimoto K, Rose JC. Atrial natriuretic factor maternal and fetal concentrations in severe preeclampsia. Am J Obstet Gynecol 1989;161:1015-9) on the plasma concentrations of atrial natriuretic peptide in patients with preeclampsia supports similar observations that we reported in such patients a couple of years ago.[1] In addition to measuring plasma atrial natriuretic peptide concentrations in patients with preeclampsia, we also measured the plasma concentrations of arginine vasopressin.

Contrary to our expectations, which were based on previously published data that indicated a contracted plasma volume in patients with preeclampsia,[2] we found that the plasma arginine vasopressin concentrations in our preeclamptic patients were not significantly different from those of the control population. Therefore the elevated atrial natriuretic peptide levels in preeclamptic patients are most likely because of left atrial distension as a result of systemic hypertension and not because of volume overload in these patients. Similarly, plasma arginine vasopressin levels in our preeclamptic patients with presumed contracted plasma volume were not elevated, also because of the postulated left atrial distension. This left atrial distension would negate any stimulatory effect of the contracted plasma volume status on release of arginine vasopressin in these patients.

It is also unlikely that the elevated plasma atrial natriuretic peptide levels in patients with preeclampsia are significantly due to diminished clearance of the peptide. Atrial natriuretic peptide is cleared not only by the kidneys but also by the liver and skeletal muscles[3] and none of the patients with preeclampsia who we studied showed any significant hepatic or renal function impairment.

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Response declined

Pregnancy loss terminology

*To the Editors:*We support Drs. Pridjian and Moawad (Pridjian G, Moawad AH. Missed abortion: Still appropriate terminology? Am J Obstet Gynecol 1989; 161:261-2) in their recommendation to change the terms used to categorize pregnancy loss. The term *missed abortion* does nothing to define the gestational age or possible cause of pregnancy loss and is no longer used in our clinic. Moreover, the arbitrary designation of "spontaneous abortion" as a pregnancy loss of <20 weeks' gestation is no longer clinically useful. Like the authors, we attempt to define pregnancy loss ultrasonographically as either an anembryonic gestation (blighted ovum) or fetal death (first or second trimester). A precise history of previous pregnancy losses

should also be obtained. It is often helpful to determine whether the patient or her doctor heard the fetal heart rate with a Doppler device or stethoscope. Some patients recall seeing a fetus, indicating that the loss was not an anembryonic gestation. Often, however, (especially with first trimester losses), neither the patient history nor the available records indicate whether a fetus was present. An appropriate term for this type of pregnancy loss is *spontaneous abortion, fetal status unknown.*

Early pregnancy ultrasonography may provide prognostic information. In normal women with uncomplicated pregnancies, the presence of a live fetus in the first trimester predicts a very low rate of subsequent pregnancy loss (<4%).[1] Among otherwise normal women with threatened abortion, the presence of a live fetus by first- or early second–trimester ultrasonogram suggests a subsequent loss rate <15%.[2, 3] But similar prognostic data are not available for women with recurrent pregnancy loss, and the utility of first-trimester ultrasonography in such patients remains undefined. For women with recurrent pregnancy loss, systematically gathered, prospective data are needed to determine how first-trimester ultrasonography might be useful in defining the cause of pregnancy loss and the prognosis in the current pregnancy.

We disagree with Drs. Pridjian and Moawad on one point made in their Clinical Opinion article. They recommended that the physician should "promptly" schedule dilatation and curettage if "nonviability of a pregnancy is ascertained." According to the scheme they outlined, "nonviability" would be diagnosed when "at ≥7.5 weeks there is no fetus." One should be cautious about immediate evacuation of the uterus with an empty gestational sac ≤8 weeks' size. In our experience this would occasionally have led to the termination of a normal pregnancy. In some cases it may be better to repeat the ultrasonographic evaluation 5 to 7 days later to exclude inaccurate measurements and to confirm that the gestation is truly anembryonic.

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Reply

To the Editors: We appreciate the comments of Drs. Branch and Scott, who are in general agreement with our proposed change in terminology.

We share their concern that one should be cautious in immediate evacuation of the uterus with an empty gestational sac ≤8 weeks' size. However, the ability to see the fetal pole in a normal pregnancy at 7½ weeks gestation is equipment dependent. In our institution the lack of a fetal pole at ≥7½ weeks' gestation is diagnostic of an anembryonic, abnormal gestation. Timor-Tritsch et al.[1] stated that with the use of a 6.5 MHz transvaginal mechanical sector scanner, at 6½ weeks (one week earlier to our proposed 7½ weeks), not only should a fetal pole be seen, but a heartbeat must be seen.[1] Clinicians should be familiar with the ultrasonographic capabilities in their respective institutions and practice accordingly. Patients with insulin-dependent diabetes may require repeat scanning because investigators suggest their fetuses may show a growth delay.[2]

Undoubtedly, if there is any concern with accuracy or capabilities of ultrasonographic diagnosis, unsure dates, or potential growth delay, the prudent course of action, as noted in the footnote in our scheme, would be to repeat the scan.

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Sapphire probes in obstetric laser surgery

To the Editors: In their brief report on death caused by embolism with hysteroscopic intrauterine surgery performed with a neodymium: yttrium-aluminum-garnet (Nd:YAG) laser (Baggish MS, Daniell JF. Death caused by air embolism associated with neodymium:yttrium-aluminum-garnet laser surgery and artificial sapphire tips. Am J Obstet Gynecol 1989;161:877-8) the authors concluded that "use of sapphire tips for intrauterine laser surgery is associated with grave hazards for the patient." Unfortunately, this conclusion is unwarranted. First, in both cases room air was used as a coolant for the distal probe. Use of room air is contraindicated for any hysteroscopic procedure because of the danger of gas embolism compared with use of carbon dioxide, which is much more soluble in blood. Even so, the flow rate of carbon dioxide used to cool the sapphire probes can easily be in excess of 1 L/min, clearly not a safe level of flow within the uterus, the vascular tree of which can quickly absorb enough carbon dioxide to cause systemic acidosis, leading to cardiac arrhythmia even if the solubility of carbon dioxide in blood is not exceeded.

There is a legitimate role for use of the sapphire tips in intrauterine operations, including incision of the uterine septum and submucous myomectomy. Because of the small volume of the uterus and production of some smoke, this cannot conveniently be done with carbon dioxide distention of the uterus. Therefore it must be performed with some liquid medium as a distending source. Under those circumstances, the tip may be cooled with a liquid because gas causes bubbles to form in the distending medium. There is no reason to use the sapphire probe for endometrial ablation where the scatter effect of the bare fiber is desired. The fiber needs no cooling flow.

To indict the sapphire tip in intrauterine operations is to focus on the most obvious suspect, but misses the actual mechanism by which the untoward effect is generated.

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Reply

To the Editors: We appreciate Dr. Corson's interest in our communication in brief in which we reported two deaths related to the use of artificial sapphire tips. Both deaths were associated with intrauterine operation performed with the Nd:YAG laser via coaxial fiber-sapphire probes (tips). Unfortunately, space limitations prevented us from relating the details of the grievous injuries inflicted on other patients by the use of these devices. The full scope of these catastrophies has been reported subsequently.[1] Recently, even another death occurred with the use of sapphire tips in a general surgery procedure. The magnitude of these tragic outcomes is particularly odious when viewed in the context of the admirable safety record associated with the general applications of lasers in gynecology. Contrast the lopsided volume of cases safely performed with carbon dioxide, argon, KTP 532, and bare fiber–delivered Nd:YAG lasers with the minuscule number performed with Nd:YAG laser–ensembled sapphire tips. This disparity is more blatant when coupled with the appalling number of mortalities associated with the latter technology.

Clearly any gas, including carbon dioxide, should be used with trepidation for cooling sapphire tips. Curiously, within the past month a widely read publication described the option of gas cooling at flow rates ranging between 20 and 30 ml/sec, which translates to 1200 to 1800 ml per minute.[2] Because the sapphire tip must make contact with the tissue to effect an action, the coolant gas enfilades the disrupted stromal planes and seeps into vascular spaces. This phenomenon creates circumstances favorable for lethal carbon dioxide gas embolus.

None of our reported cases occurred before 1986, and one case occurred as late as 1988. Nevertheless, even today surgeons and gynecologists continue to use gas to cool the tips. Although these ephemeral devices offer few compelling advantages, we agree that if they must be used, they should always be cooled with water or saline solution. In regard to the examples referred to by Dr. Corson, it is our belief that the Nd:YAG laser delivered by a bare fiber is superior to a sapphire tip both in its simplicity and superior hemostasis for the hysteroscopic treatment of submucous uterine myoma.[3] Uterine septa may be cut hysteroscopically by scissors or alternatively by the Nd:YAG laser with bare, extruded fibers, or with other fiberoptic lasers.[4]

The message we convey is that further animal studies and carefully designed clinical trials are required to detect *every* dangerous aspect of these sapphire devices. Technologic preferences must always take a second berth when questions of patient safety exist.

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Epidural analgesia and cesarean section for dystocia

To the Editors: I read with interest the recent report by Thorp et al. (Thorp JA, Parisi VM, Boylan PC, Johnston DA. The effect of continuous epidural analgesia on cesarean section for dystocia in nulliparous women. AM J OBSTET GYNECOL 1989;161:670-5). The authors stated that "there are many mechanisms by which epidural analgesia could increase the incidence of cesarean section for dystocia." Since the authors believe that there are "many mechanisms," it is surprising that they listed only three.

1. The authors suggested that "a decrease in uterine activity without appropriate intervention with oxytocin could result in more cesarean sections for dystocia." This seems irrelevant to their study because all patients were managed "according to the principles of active management of labor."
2. The authors suggested that "relaxation of the pelvic diaphragm could predispose fetuses in a cephalic presentation to minor malpresentations such as occipitoposterior, deflexion, and asynclitism." But the authors did not compare the epidural and nonepidural groups with regard to incidence of abnormal position of the vertex. Even

if the authors had documented an increased incidence of abnormal position in the epidural group, they should have also considered the possibility that the abnormal position preceded (or even prompted) the use of epidural analgesia.

3. The authors stated that "epidural analgesia could decrease the maternal stimulus and ability to push during the second stage." It is not clear whether this potential mechanism is relevant to their study because they did not report the incidence of cesarean section for second-stage dystocia in the two groups. This suggestion is in conflict with the results of two prospective, randomized studies[1,2] in which nulliparous patients receiving epidural analgesia were randomized to receive additional local anesthetic or saline solution–placebo after 8 cm of cervical dilation. Women who continued to receive local anesthetic until delivery were *not* more likely to undergo cesarean section than women who received the placebo.[1,2]

The authors failed to substantiate any mechanism(s) by which epidural analgesia could have increased the incidence of cesarean section in their patient population. The use of multivariate analysis notwithstanding, the major problem with any nonrandomized assessment of the influence of epidural analgesia on the method of delivery is the potential for selection bias. Why do some, but not all, nulliparous women request and receive epidural analgesia during labor? The authors did not acknowledge the possibility that the very reason(s) why some, but not all, parturients request and receive epidural analgesia may relate to a greater likelihood of abnormal labor and increased risk for cesarean section. The authors suggested that "ethical considerations" would preclude the performance of a prospective study in which nulliparous patients are randomized to receive or not receive epidural analgesia during labor. In my judgment, this betrays a lack of conviction. For example, "ethical considerations" have not precluded the performance of studies in which patients were randomized to undergo electronic fetal heart rate monitoring or intermittent auscultation. If use of epidural analgesia increases the incidence of cesarean section for dystocia, it should be confirmed in an appropriate scientific study. But what if the use of epidural analgesia does not increase the incidence of cesarean section? Nonrandomized studies such as theirs may inappropriately discourage obstetricians and patients from use of the most effective method of intrapartum analgesia.

I acknowledge that prospective, randomized studies are difficult and tedious. But results of nonrandomized studies such as this one cloud rather than clarify the issue. I urge the authors and others to perform prospective studies that provide more meaningful information regarding the relationships between epidural analgesia and the method of delivery.

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Reply

To the Editors: We appreciate Dr. Chestnut's interest in our research. Indeed, "There *are* many mechanisms by which epidural analgesia could increase the incidence of cesarean section for dystocia."[1] The following potential mechanisms have a basis in the literature: (1) decrease in uterine activity; (2) prolongation of first stage of labor; (3) relaxation of pelvic diaphragm, therefore predisposing to minor malpresentation; (4) decrease in maternal urge to push; (5) decrease in maternal ability to push; (6) prolongation of second stage of labor; (7) increased risk of instrumental vaginal delivery, which is less likely to be pursued for medicolegal reasons.

This investigation was not designed to ascertain the exact mechanisms operative in our study. However, any one or combination of the above mechanism(s) could easily account for the increased incidence of cesarean section associated with epidural in our study.

Dr. Chestnut readily cites his own two randomized prospective studies that suggest that use of epidural anesthesia does not increase the incidence of cesarean section.[2,3] Unfortunately, both the experimental and control groups in these studies[2,3] had epidural anesthesia until 8 cm of cervical dilatation and then were randomized to receive either placebo or a local anesthetic agent through the epidural catheter. Therefore these studies[2,3] did not assess the significant effect of epidural anesthesia before 8 cm of cervical dilatation. In fact, when both studies[2,3] are combined, the majority of cesarean sections (11/19) were excluded because they were performed before 8 cm of cervical dilatation. We disagree with Dr. Chestnut's conclusion that use of epidural anesthesia does not increase the overall incidence of operative delivery because he excluded most of his cesarean sections.

Many studies conclude that the frequency of instrumental delivery increases with epidural analgesia.[4] Since many obstetricians are less likely to attempt forceps delivery because of medicolegal concerns, an increase in cesarean section results. Dr. Chestnut continues to argue that use of epidural analgesia does not cause an increase in forceps delivery.[5] This is interesting in view of his own randomized prospective study that unequivocally demonstrated that epidural analgesia does increase forceps delivery (21/40 vs 11/40, $p < 0.05$).[2]

Dr. Chestnut is concerned because our retrospective study[1] may "inappropriately discourage obstetricians and patients from using the most effective method of

intrapartum analgesia." We remind Dr. Chestnut that there are many institutions in the United States and in other countries that continue to do well without intrapartum epidural analgesia and in fact have quite low cesarean section rates. Of more concern to us is the possibility that there may be many unnecessary cesarean sections because of epidural analgesia, perhaps not at the University of Iowa, but at other hospitals that do not have the interest, understanding, and expertise of Dr. Chestnut.

We agree with Dr. Chestnut in that prospective studies are superior to retrospective studies, and need to be performed. We do not think that our ethical considerations portray a "lack of conviction" on our part. We have no ethical concerns with Dr. Chestnut's prospective studies. However, to accurately assess the effect of intrapartum epidural on cesarean section rates, patients must be randomized to "epidural" and "no epidural groups" before labor or in early labor. This is the study that should be done, and it would pose significantly different ethical concerns than those of Dr. Chestnut's studies.[2, 3] We wholeheartedly encourage such a study and think that our retrospective studies will lend further support for an investigational research board approval.

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Accuracy of apical four-chamber view as screen for congenital heart disease

To the Editors: Please allow me to recount a recent experience of the usefulness of the apical four-chamber view of the heart as a screening test for congenital heart disease in pregnancy.

A 23-year-old patient had one of the first early repairs of a congenital heart defect of severe endocardial cushion disorder at 5 years of age. After operation she required permanent installation of a pacemaker. The patient was first seen at 23 years of age, married with an elective pregnancy 15 weeks from the last menstrual period and requesting a "reassurance" fetal health check.

A detailed fetal anatomy survey revealed no abnormalities of the head, body, spine, arm, legs, and feet; measurements were consistent with dates. The patient was previously immunized with rubella titer. We were unable to obtain an apical four-chamber view of the heart. Ultrasonography of the heart was repeated 5 days later with the assistance of a pediatric cardiologist experienced in fetal echocardiography, by dates and ultrasonographic size at 16 weeks of gestation.

A detailed fetal heart evaluation with multiple scan planes of orientation confirmed abnormal heart anatomy with a delineation of the right ventricle with pulmonary outflow tract well visualized, right atrium, left atrium, hypoplastic left ventricle (none seen), atresia of the aortic root, and aortic arch.

Genetic amniocentesis was performed. However, on the basis of the abnormal ultrasonographic findings, the couple elected genetic termination of pregnancy. Verification of the heart anomaly was not possible by dilatation and evacuation; chromosomes were normal.

This case has several interesting aspects. It demonstrates that it is possible to screen for significant severe (in this case, fatal) congenital heart defect(s) by the inability to obtain a "normal four-chamber image."[1] It further shows continuing improvement in the sensitivity that can be achieved, particularly from the continuing improvements in real-time ultrasound imaging (equipment used: General Electric model RT 2800, recently upgraded to 3200, with a 5.0 MHz curve probe). In this case, this sensitivity and the specificity that was obtained both by the initial four-chamber view screening examination followed by the detailed fetal echocardiographic evaluation, permitted early prenatal diagnosis and enabled the couple to exercise their reproductive option while still in the early second trimester of pregnancy.

The recurrence risk for endocardial cushion defect is said to be 2.9%.[2] It is usual to give couples, when the mother herself has a congenital heart defect, an empirically derived recurrence risk of 10% to 15%. Nora[3] states "A major concern in ECD is that when it is familial, it may be high-risk [type C or Mendelian]. Therefore, we give a low recurrence risk of 2% if there is one effected first degree relative, but a high risk [50%] if there are two first degree relatives with the disease."

For this couple, in the next pregnancy prenatal diagnosis genetic counseling recurrence risk must be considered to be 50%, and they were so apprised of that high-level risk.

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Is meconium aspiration an intrauterine event?

To the Editors: The report of Rossi et al. (Rossi EM, Philipson EH, Williams TG, Kalhan SC. Meconium aspiration syndrome. Intrapartum and neonatal attributes. AM J OBSTET GYNECOL 1989;161:1106-10) describing intrapartum factors that could assist the obstetrician in prediction of the occurrence of meconium aspiration syndrome prompted us to review similar published work in this critical area. During the last few years the obstetric and pediatric community believed that meconium aspiration syndrome could be prevented. This belief was based on (1) the assumption that meconium aspiration is a postnatal event, (2) that nasal-oropharyngeal DeLee suctioning of meconium before the delivery of the chest as described by Carson et al.[1] should prevent meconium from being drawn into the tracheobronchial tree during the first few breaths, and (3) the excellent results obtained with this technique by Carson at her institution. However, although no one has yet confirmed their work, the paper has become a landmark document when meconium aspiration syndrome developed in infants. Lawyers have extensively used it to prove that if the meconium aspiration syndrome developed, it was because of lack of adequate suctioning by the obstetrician.

The work by Rossi et al. provides us with data to support the possibility of an intrauterine mechanism of meconium aspiration. Among the 16 infants with aspiration of "thick" meconium, 50% (eight infants) did not "breathe" before intubation and suctioning in the delivery room. If they did not cry or breathe before suctioning, then we could speculate that meconium was below the vocal cords before delivery. Ten of 22 infants with meconium aspiration syndrome did not breathe before intubation and suctioning. If their airways were properly suctioned before the delivery of the chest, it is unlikely they aspirated meconium after birth, supporting the hypothesis that meconium aspiration is an intrauterine event. Intrauterine aspiration may be the rule rather than the exception. Four infants died as a result of severe meconium aspiration syndrome and persistent pulmonary hypertension despite suctioning with a DeLee apparatus and endotracheal suctioning of the upper airway. Suctioning failed to prevent meconium aspiration syndrome and persistent pulmonary hypertension in this study.

Our previous work[2] prospectively studied the effect of DeLee and tracheal suctioning on the incidence of meconium aspiration syndrome. In a series of 755 infants with meconium-stained fluid born during the 12 months of the study year (1983), the incidence of meconium aspiration syndrome was 2% and DeLee tracheal suctioning was routine. This incidence was not different from that seen in a retrospective review of a similar group of 742 infants born in a previous year (1975) when such suctioning was not routine. Suctioning did not prevent meconium aspiration syndrome or persistent pulmonary hypertension.

According to Rossi et al., "A history of thick meconium, the absence of fetal cardiac accelerations and tachycardia on FHR monitoring, umbilical artery pH $\leq$ 7.15, Apgar scores $\leq$5 at 1 and 5 minutes and meconium in the trachea correctly predicted 50% of the infants who require neonatal intensive care unit admission for meconium aspiration syndrome." I suggest a different interpretation of their data. Their aim was to identify predictors for meconium aspiration syndrome, but the factors they identified as predictors of meconium aspiration syndrome are, indeed, consequences of meconium aspiration syndrome. These predictors are actually clinical indicators that meconium aspiration syndrome is present at birth and probably began in utero. In our study,[2] we estimate that during the study year meconium aspiration syndrome developed in 75% of infants while still in utero. In utero aspiration could provide an explanation why meconium aspiration syndrome is not completely preventable despite routine DeLee suctioning.

In summary, we agree with the data of Rossi et al. and only disagree in the interpretation of their findings. We believe their data further support that meconium aspiration syndrome is a prenatal rather than a postnatal event. This concept has medical-legal implications. It should help to dispel claims by plaintiffs' attorneys that meconium aspiration syndrome is "always" a result of inadequate obstetric and/or pediatric suctioning at birth. Thus meconium aspiration syndrome is a disease that cannot always be prevented because its pathophysiologic characteristics are still not completely understood.

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Reply

To the Editors: We agree with Dr. Falciglia and would like to reemphasize that meconium aspiration syndrome does not necessarily occur after birth and thus cannot be entirely prevented by clearing of oropharynx or suctioning "below the cords" at birth. Our study and that of Dr. Falciglia have demonstrated that, particularly in the severe cases, meconium aspiration syndrome with respiratory decompensation occurred despite appropriate clearing of infant's airway at birth. All these indications point to the occurrence of meco-

nium aspiration before birth—in utero. Dr. Falciglia disagrees with our interpretation of data. We do not believe that there is any disagreement. According to our data, a history of thick meconium, the absence of fetal cardiac acceleration, fetal tachycardia, a low cord pH, and low Apgar scores indicate that intrauterine fetal distress has occurred with aspiration of meconium and that the syndrome of meconium aspiration with respiratory compromise will develop in 50% of such infants. Thus the disagreement is only in semantics rather than the concept of aspiration of meconium in utero.

We believe that these concepts are very important, both from the medicolegal viewpoint and for the clinical care of these infants.

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Cefotetan and the lack of associated bleeding

To the Editors: Although methods designed to decrease excessive hospital and patient costs are necessary and we admire the attempt by Briggs et al. to evaluate the necessity of aminoglycoside levels in the postpartum woman (Briggs GG, Ambrose P, Nageotte MP. Gentamicin dosing in postpartum women with endometritis. Am J Obstet Gynecol 1989;160:309-13), their conclusions are not valid because of limitations in the study design.

Nephrotoxicity and ototoxicity are serious consequences of elevated or prolonged aminoglycoside serum concentrations, and these problems have been well-documented.[1,2] Fortunately, they occur only rarely and can usually be prevented through careful monitoring of serum levels and renal function.[3]

For a predominantly healthy population, such as postpartum women, the incidence of renal, and to a lesser extent, auditory dysfunction, secondary to toxic aminoglycoside is rare and is estimated at maximum to be in the order of 1 in 50 and 1 in 100, respectively.[4] A statistically significant difference between two regimens attempting to evaluate protocols monitoring such toxicity would require a minimum of 2,220 and 4,507 patients, respectively, (to discover a doubling of toxicities with a p value of <0.05 and power of 80). Therefore the conclusions by the authors that the monitoring of serum aminoglycoside levels is unnecessary cannot be substantiated by the number of patients evaluated in their study.

In the 60 patients evaluated, five patients with elevated aminoglycoside levels and the threat of renal damage would have been needed to demonstrate a significant difference (Fisher's exact test). The definition of renal dysfunction is poorly defined in the study and does not state if patients with diabetes or preeclampsia are to be included in their new proposal. Thus, although we agree with the authors that the risks are low and expenses appear prohibitive, the abandonment of aminoglycoside serum measurements is as yet unsubstantiated, with potentially dangerous consequences. We wonder if the authors would have drawn the same conclusion if permanent deafness or severe renal toxicity necessitating lifelong dialysis had developed in the sixty-first patient enrolled.

Perhaps the answer to the expense of monitoring is to avoid or limit use of aminoglycoside, either by proper culturing of infected sites to document the need for aminoglycoside use or with further investigation into the utilization of several of the extremely effective broad-spectrum cephalosporin or monobactam agents.

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Reply

To the Editors: Faro and Martens' comments on patient safety are legitimate concerns and we welcome the opportunity to respond to these issues. However, we can find no evidence, either in our patients or in the literature, that otherwise healthy postpartum women with endometritis suffer a 1% to 2% incidence of renal or auditory toxicity when treated with short courses of gentamicin. Moreover, our conclusions were not based on changes in serum creatinine levels, and thus the calculations made by them for sample size do not apply to our study design.

Since 1980 we have treated approximately 2000 women with gentamicin in the postpartum period. Serum creatinine values were initially obtained at the start of therapy and then every 2 days while the patient was receiving gentamicin. Approximately 5 years ago, because we had never observed a potentially toxic increase in the repeat creatinine values, we lengthened the time interval to every 3 days. Throughout this time we have used the generally accepted principle that a rise in serum creatinine of 0.5 mg/100 ml or greater from a normal baseline was an indication of nephrotoxicity.[1] Perhaps we have been fortunate, but we have yet to detect a single instance of nephrotoxicity with this criterion. In our study, 28 of 56 women had a repeat serum creatinine value determined either because therapy exceeded 3 days or because their initial creatinine value was greater than 1.0 mg/100 ml. In eight patients the repeat creatinine value was 0.1 mg/100 ml higher than the initial value, and in three patients the repeat number was 0.2 mg/100 ml higher (0.5 to 0.7 in two

and 0.7 to 0.9 in one). In seven women the repeat serum creatinine value was the same as the initial value, and in 10, the value decreased between 0.1 and 0.4 mg/100 ml. Moreover, over the past 10 years we have selectively determined gentamicin serum levels in postpartum women as specified in our study. During this period approximately 400 women have had levels determined during their therapy. None of these patients had peak or trough concentrations above 10 or 2 μg/ml, respectively.

Our experience with gentamicin dosing in postpartum women strongly supports the four conclusions of Whelton[1] in 1985, although this reference and the other three cited by Drs. Faro and Martens do not include obstetric patients. First, nephrotoxicity or ototoxicity does not occur during the first 1 to 2 days of "major overdosing" if the renal function was initially within normal limits.[1] Second, if possible, courses of aminoglycosides should be restricted to less than 10 days.[1] In our study the range of therapy in 54 patients was 1.33 to 4.42 days (mean, 2.7 ± 1.2 days). Two patients were treated for longer times: 6.32 and 6.33 days, respectively. Our practice has always been to determine levels of any patient treated for 7 days or longer. Third, in patients with normal renal function, a dose of 1 to 2 mg/kg body weight every 8 hours provides appropriate serum levels.[1] Our recommendation of 1.75 mg/kg for average-size women with documented rapid clearance fits within Whelton's range. Fourth, serum drug monitoring should be undertaken after 5 to 7 days of therapy, especially in high-risk patients, because this is when the toxic effects of aminoglycosides are most likely to occur.[1] Except that our patients were women, none could be classified as "high risk" (refer to Whelton, page 73, for his characteristics of patients with clinical risk factors for aminoglycoside nephrotoxicity).

On the basis of our 10-year experience with this patient population, and the conclusions cited in the current literature for patients in general, we believe our recommendations are valid. The use of pharmacokinetic dosing principles in these patients is the best method to ensure that appropriate doses are being administered. However, we recognize that, no matter how desirable, these methods are not always available to the clinician. Thus, rather than replace an inexpensive, effective drug with antibiotics that are much more expensive, we chose to recommend a simple, cost-effective dosing method. We do believe, however, that serum drug level monitoring is mandatory for any patient with renal impairment or abnormal vascular volumes (such as patients with diabetes and preeclampsia), for women whose body heights or weights are much different than average, and for any patient receiving gentamicin for 7 days or longer.

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Ultrasonographic guidance for central venous access

To the Editors: Lee et al. described the use of real-time ultrasonography to localize the internal jugular vein and guide the cannulation required for pulmonary artery insertion (Lee W, Leduc L, Cotton DB. Ultrasonographic guidance for central venous access during pregnancy. Am J Obstet Gynecol 1989;161:1012-3). In 1986 Yonei et al.[1] reported using this technique for 160 patients without failure or complications. The anatomy as visualized by ultrasonography was described earlier.[2] The efficacy of ultrasonographically guided cannulation of the internal jugular vein was evaluated by Mallory et al.[3] They used a 5 MHz small parts, near-focus transducer inserted into the thumb of a sterile glove, size 8½. Povidone iodine ointment was used as the acoustic coupling medium. Under ultrasound guidance 12 of 12 patients had successful catheterization whereas significantly fewer (11 of 17) had successful catheterization with the conventional technique without ultrasound guidance. The mean (±SD) number of passes to cannulate the vein was 1.7 (±0.97) with ultrasonography versus 2.94 (±1.73) without ultrasonography, a significant difference. Obstetric patients who require critical care are likely to benefit from management incorporating techniques initially described by intensivists.

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Reply

To the Editors: The additional information that Dr. Greenspoon offers through his critical care medical background is greatly appreciated. Obstetricians should be able to extend these experiences to patients who require invasive hemodynamic monitoring. This should remind perinatologists who use ultrasonographic guidance for percutaneous umbilical artery sampling that the same principles can also be applied to much larger vessels in critically ill gravid women.

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Fetal heart rate monitoring during cesarean section

To the Editors: I read with interest and dismay the article by Petrikovsky et al. (Petrikovsky BM, Cohen M, Tancer L. Usefulness of continuous fetal heart rate monitoring during cesarean section. AM J OBSTET GYNECOL 1989; 161:36-7).

In my opinion their suggestion to leave the scalp electrode attached during cesarean sections for fetal distress represents poor surgical judgment. Removing wires contaminated by stool and vaginal secretions through the uterus and maternal abdomen can only serve to increase the infection rate in the mother without demonstrable benefit to the fetus.

In the authors' first case in which the surgeons encountered extensive abdominopelvic adhesions, it is difficult for me to imagine how the operators would have responded to a decreased fetal heart rate. Would they have cut through the maternal bowel and bladder to rescue the fetus? I would hope that the surgeons exercised appropriate care and skill while progressing as rapidly as possible with the dissection, as any good surgeon would do.

In their second case, as in all cesarean sections for fetal distress, the procedure should have been done as deftly and expeditiously as possible. As the case demonstrates, the return of the heart rate to normal is not a license to dawdle.

The authors' suggestion that undue surgical haste causes fetal and maternal injury is valid. However, an experienced and competent surgeon would never move so quickly as to endanger the mother in order to deliver the fetus a few seconds sooner. It is proposals such as those made by the authors in this article that perpetuate the myth (reality?) that many obstetricians are not "real" surgeons. By rejecting their proposal, obstetric surgeons can avoid perpetuating that myth.

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Reply

To the Editors: We would like to respond to Dr. Dunn's comments.

First, we regret causing her dismay, which could have been avoided if she had read our initial publication (reference 2 in the article), from which we quote, "The lower extremities were 'frog legged' so that the scalp electrode could be removed 'from below' as the fetal vertex was about to be delivered."

Second, in case 1, had urgency been necessary, "meticulous and time-consuming surgery for identification of the vesicouterine fold and dissection of the bladder flap" would not have been carried out. A classic incision would have expedited delivery of the presumed compromised fetus.

Finally, we agree that "undue surgical haste is never wise." However, a "real" surgeon knows that there are options to any surgical approach that permit a flexible response to the needs of the moment.

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Can anesthetic-related maternal mortality be reduced?

To the Editors: anesthesia continues to be a prominent cause of maternal mortality, accounting for approximately 10% of pregnancy-related deaths.[1] At least 90% of maternal deaths are attributable to general anesthesia, primarily as a result of failed endotracheal intubation or pulmonary aspiration of gastric contents,[1] despite the fact that more than 50% of cesarean sections in the United States are performed with regional (spinal or epidural) anesthesia.[2] May and Greiss (May WJ, Greiss FC Jr. Maternal mortality in North Carolina: A forty-year experience. AM J OBSTET GYNECOL 1989;161:555-61) report comparable statistics for anesthetic-related deaths (of which *all* were attributable to use of general anesthesia) and further state that "anesthetic complications represent the most clearly identifiable area for prevention." I certainly agree with this viewpoint, but I would like to comment on a statement by Dr. J. Bruce Taylor in the Discussion section of this article.

Dr. Taylor stated that "We may very well have reached an irreducible minimum in anesthetic-related deaths with more complications occurring now from morbid obesity than from the gravid state. (Three of four deaths were noted in markedly obese patients.)" This contention is supported by May and Greiss, who found no change in deaths from anesthetic complications from 1981 to 1985 compared with 1976 to 1980. However, I think that increased use of regional anesthesia, which rarely results in maternal mortality, will almost certainly reduce the number of deaths from anesthesia because regional anesthesia does not eliminate the parturient's ability to protect her airway from pulmonary aspiration of gastric contents and obviates the need for endotracheal intubation (for which failure to accomplish the procedure, in obstetrics, has been reported to occur in 1 in 300 attempts,[3] with difficulty encountered in 5% of cases[4]). I also believe that the morbidly obese parturient is especially suited for regional anesthesia.

Obese individuals, because of more difficulties with intubation and higher gastric volume, lower gastric pH, and diminished barrier pressure (lower esophageal sphincter tone minus intragastric pressure) compared with normal patients, are exposed to much greater risks during general anesthesia.[5] The fact that three of the four anesthetic-related deaths reported by May and Greiss resulted from difficult endotracheal intubations in markedly obese individuals attests to the anesthetic

risks involved. I believe, as do others,[5] that regional anesthesia (specifically epidural anesthesia) is the technique of choice for cesarean section in the obese parturient. In addition to eliminating the risks of inducing unconsciousness and performing endotracheal intubation, use of regional anesthesia reduces postoperative pulmonary complications in obese patients.[6] Intraspinal narcotics can be used, and obese individuals who receive epidural narcotics for postoperative analgesia ambulate earlier, suffer fewer pulmonary complications, have shorter hospital stays,[7] and have less respiratory depression than patients who receive parenteral narcotics.[8]

Another situation in which I think increased use of regional anesthesia is appropriate is that of emergency cesarean section for fetal distress. Although many clinicians favor general anesthesia in this situation, use of regional anesthesia (epidural via a catheter already in place, or spinal) results in equivalent or better neonatal outcome, despite the fact that institution of regional anesthesia may (but not necessarily) take longer.[9-11] This is probably because of the fact that general anesthesia compromises uterine blood flow and fetal well-being,[12] in association with enhanced maternal sympathetic nervous system activity from endotracheal intubation[13] and maternal cardiovascular depression from the thiobarbiturate,[12] whereas regional anesthesia blocks sympathetic nervous system activity and improves uterine blood flow (provided adequate fluid preloading is used).[14]

Increased use of spinal and epidural anesthesia for cesarean section should have a favorable impact on anesthetic-related maternal mortality. In my opinion, regional anesthesia is the technique of choice in all situations (including emergency cesarean section and for the morbidly obese parturient) unless an absolute contraindication exists (coagulopathy, infection over the site of needle puncture, maternal hemorrhage with hemodynamic instability, or patient refusal).

Finally, May and Greiss stated that "such circumstances demand the best anesthesia expertise available," referring to anesthetic management of the obese parturient. This statement certainly applies equally to any obstetric anesthetic administered.

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Ritodrine infusion and cardiomyopathy

To the Editors: Blickstein et al. (Blickstein I, Zelel Y, Katz Z, Lancet M. Ritodrine-induced pulmonary edema unmasking underlying peripartum cardiomyopathy. AM J OBSTET GYNECOL 1988;159:332-3) have reported a case of cardiomyopathy associated with pulmonary edema in a woman receiving ritodrine. In the patient described ritodrine was infused intravenously at rates of 50 to 100 μg/min continuously for 28 days. No reference was made to evaluation of fetal lung maturity. At 34⅚ weeks, when contractions recurred, the ritodrine infusion rate was increased to 300 μg/min and 3 hours later pulmonary edema developed.

There are several aspects of this case that merit consideration. First, in the case presented, the authors have referred to the cardiomyopathy in this case as being idiopathic in nature. However, it is equally possible that prolonged ritodrine infusion altered myocardial function, leading to the clinical picture of a cardiomyopathy. Catecholamines infused for prolonged periods or in high doses can cause myocardial necrosis and cardiomyopathy.[1,2] Therapeutic concentrations of

β-adrenergic receptor stimulations in vitro or in vivo cause specific lesions in human fetal or neonatal myocardium.[3, 4] In view of these observations one cannot exclude the possibility that myocardial dysfunction in this patient was caused by rather than unmasked by prolonged ritodrine infusion.

A second aspect of this case relates to the aggressive use of ritodrine or any tocolytic. Is it appropriate to infuse a drug such as ritodrine continuously for 28 days? Is it appropriate to attempt to reinhibit labor in a patient such as the one described, who has recurrent labor at 34⅚ weeks? The authors indicate that three attempts were made to switch to oral ritodrine after the first episode of preterm labor was treated with intravenous medication. The authors do not indicate the dosage of oral ritodrine used in this transition. We have shown in pregnant women that peak plasma concentrations of ritodrine after a 20 mg dose average only 8 ng/ml, yet the concentration achieved during an infusion of 50 μg/min is approximately 23 ng/ml.[5, 6] Thus, when oral ritodrine therapy is used to sustain labor inhibition after intravenous infusion, recurrent labor can occur since the plasma concentrations during oral therapy are much lower than after intravenous therapy. Even with repeated oral doses of 20 mg, the peak and trough concentrations of ritodrine are only 18 and 11 ng/ml, respectively.[7] These concentrations are unlikely to sustain labor inhibition, and, as we have demonstrated, a ritodrine dose of 20 mg every 4 hours is significantly less effective in this regard than is terbutaline 5 mg every 4 hours.[5] We[8] and others[9] have documented that administration of β-agonists for prolonged periods leads to a rapid loss of myometrial β-adrenergic receptors and a loss of tocolytic efficacy. These receptor effects coupled with a dosage regimen that provides low plasma concentrations place the patient at high risk for recurrent labor.[5] These circumstances also may account for the inability to "wean" patients from parenteral to oral therapy. Rather than using higher oral doses, some physicians have chosen to administer a tocolytic agent intravenously for prolonged periods. The risks associated with such therapy have not been adequately evaluated. Besides producing metabolic and cardiovascular derangements, which have been characterized with short infusions, prolonged infusion of these agents may produce other effects such as the one described by Blickstein et al. Also the impact of prolonged bed rest must be assessed, particularly in view of the known effects of bed rest on bone demineralization, muscle wasting, thromboembolic disease, and maternal emotional and psychological state. The case presented by Blickstein et al. suggests that overly aggressive use of tocolytic agents should be discouraged.

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Reply

To the Editors: We thank our distinguished Pittsburgh colleague for the informative critique. He suggests an alternative explanation for cardiac failure, namely, secondary cardiomyopathy allegedly caused by ritodrine cardiotoxicity. He cited sympathomimetic-induced cardiac necrosis and myopathy with rather nonspecific agonists or with ritodrine itself on immature fetal and neonatal tissue. However, there are no similar reports in adult or pregnant patients. On the other hand, several studies evaluated echographically the cardiovascular effects of ritodrine tocolysis. Hosenpud et al.[1] studied the left ventricular size and performance during ritodrine tocolysis and found that left ventricular end-diastolic dimensions were unchanged. M-Mode echocardiography performed before and during intravenous β-adrenergic agonist tocolysis found decreased left ventricular dimension and no changes in left atrial dimension.[2] Hadi et al.[3] found similar cardiovascular effects. Interestingly, in half of the patients in the latter study, pulmonary capillary pressure exceeded the threshold for the development of pulmonary congestion but none had clinical manifestations. It is therefore expected that some evidence of dilative cardiomyopathy has to be seen before ritodrine is included among

the potentially cardiotoxic agents (such as the anthracycline doxorubicin, high-dose cyclophosphamide, 5-fluorouracil, tricyclic andidepressants, and lithium. None has been observed thus far.[1-3]

Next, the commentator questions the logic in prolonged intravenous ritodrine treatment. There is no doubt that myometrial adrenergic receptor desensitization does occur. Using the lowest effective ritodrine dose titrated clinically to the presence of uterine contractions and maternal tolerance, we are able to arrest labor effectively without monitoring plasma levels of ritodrine, as described in our case report. In our exceptional case, cardiac deterioration must have been insidious and probably unpredictable. In a similar case, subendocardial ischemia on electrocardiography that was found during ritodrine tocolysis resulted from a large left atrial myxoma.[4] Obviously, in both cases ritodrine alone could be blamed for the cardiac complication and the correct diagnosis would have been missed without echocardiography.

The dangerous connotation attributed by the commentator to aggressive use of tocolytic agents must be seen in proportion. There is certainly no place for injudicious and unattended ritodrine treatment. In contrast, careful patient selection combined with intensive monitoring[3] may result in higher rates of successful labor arrest with rare cases of severe side effects.

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Ethics and routine ultrasonography in pregnancy

To the Editors: We disagree with the opinion of Chervenak et al. who argue that prenatal informed consent for sonogram should become an accepted indication for obstetric ultrasonography (Chervenak FA, McCullough LB, Chervenak JL. Prenatal informed consent for sonogram: An indication for obstetric ultrasonography. Am J Obstet Gynecol 1989;161:857-60). After listing our arguments against this proposal, we also direct their and the reader's attention to a randomized trial of routine ultrasonography that we are conducting.

In our experience the majority of patients accept the offer of an ultrasonographic examination. The policy of offering ultrasonography routinely is undesirable for several reasons. The first and most important is that its value in low-risk pregnant women and their infants is unclear. Second, there are potential disadvantages, including false-positive diagnoses and the theoretical risk of adverse bioeffects. Finally, standards of care that are based on patient autonomy in the absence of established benefit create unrealistic expectations of physicians and the health care system, lead to inappropriate legal liability, and may eventually prove to be harmful to patients.

We will briefly expand on these points in turn, starting with the value of routine ultrasonography. The authors state that "established benefits currently outweigh harms" and quote several descriptive studies that report diagnostic advantages of routine ultrasonography. However, they do not refer to six published clinical trials that fail to convincingly demonstrate an improvement in perinatal outcome attributable to routine ultrasonography.[1-6]

Second, with regard to possible harm, current epidemiologic research on ultrasonographic bioeffects is inadequate to rule out adverse consequences of fetal ultrasound exposure. Although we assume that ultrasonography is safe, the lack of direct evidence linking human fetal ultrasonographic exposure with adverse outcomes in existing studies cannot be interpreted to mean that there is no risk.[7,8] Until benefit is shown, this theoretical risk must be considered.

In addition to potential bioeffects, false-positive diagnosis and misdiagnosis with ultrasonography can lead to anxiety and unnecessary intervention. Case reports of misdiagnosis of congenital anomalies illustrate the importance of accuracy in prenatal ultrasonography.[9] Mistakes are more likely in the general use of ultrasonography since accuracy is expected to be less than that reported by experts. Also, the predictive value of a positive test is lower in screening programs because of the low prevalence of abnormalities in low-risk populations.[10]

Finally, if we accept the authors' argument that routine ultrasonography should be offered with informed consent, then the same reasoning should apply in other circumstances. The logical extension of this reasoning is that all diagnostic procedures and therapeutic interventions of uncertain value should be offered to each asymptomatic, apparently healthy patient provided they are believed to be without significant risk. Furthermore, physicians could be legally liable for not doing so. Neither physicians nor the health care system could possibly meet this expectation. Even if they could, it may result in harm for patients. Rather, we agree with Elias and Annas[11] that "the welfare of individual patients remains the central concern in the setting of practice standards."

One of the authors' rationales for invoking the principle of autonomy to justify offering every patient an ultrasonographic examination is the assumption of

Chervenak et al. that "conclusive scientific data" on its value is not available now nor will it be "in the foreseeable future." We are attempting to produce conclusive scientific data on the value of routine ultrasonography. The Study of Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) is a multicenter, randomized clinical trial comparing routine ultrasonography with usual prenatal care. RADIUS is funded by the National Institute of Child Health and Human Development. The primary aim of RADIUS is to determine the impact of routine ultrasonography on perinatal morbidity and mortality. The trial is designed to avoid the methodologic deficiencies of previous trials, particularly inadequate sample size and the use of ultrasonographic examinations with limited content by inexperienced ultrasonologists.[12] As of this writing, we have randomized approximately 65% of the 15,500 patients we estimate that we need for our study. Our hope is that the RADIUS trial will provide evidence needed to resolve the current uncertainty about routine ultrasonography.

If research can establish a beneficial impact of routine ultrasonography on pregnancy outcome, then physicians should offer it to their patients (including discussion of the potential benefits and risks). Until then, we continue to agree with the conclusions of the National Institutes of Health Consensus Conference on Ultrasound Imaging in Pregnancy and the American College of Obstetricians and Gynecologists that a critical review of the scientific evidence indicates that the value of routine ultrasonography is unclear.[13, 14] These authors' ethical argument that patient autonomy justifies offering ultrasonography routinely would lead to unrealistic expectations of physicians and the health care system, cause an inappropriate legal liability, and may be harmful to patients. It would be ironic and inappropriate to create a standard of care that obligates physicians to offer their patients a procedure of uncertain value when the obligation to provide access to basic prenatal care to all women has not yet been accepted in our society.

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Reply

To the Editors: We appreciate the interest of Ewigman et al., who raise a number of criticisms of our proposal that prenatal informed consent for sonogram (PICS) should become an accepted standard for obstetric ultrasonography. We believe that these criticisms can be successfully addressed.

First, we did not make direct reference to the six published articles because of limitations on the number of references in a Clinical Opinion article. We referred to the largest series in the literature.

Second, these trials and the approach of Ewigman et al. focus only on certain beneficence-based clinical considerations, for example, improvement in perinatal outcome. They neglect the importance and relevance of the ethical principle of respect for autonomy, and therefore of enhancing the autonomy of pregnant women. Thus their approach is conceptually incomplete from the perspective of ethics.

Third, we do consider the risks of ultrasonography and argue that, when considered in contrast to the benefits of routine ultrasound, the beneficence-based *balancing* of risks and harms is uncertain. The risks are theoretical, whereas the benefits that we identify can be established independently of the RADIUS clinical trial (e.g., detection of many unsuspected fetal anom-

alies in time to affect obstetric management[1, 2]). We argue that when the beneficence-based balancing of benefits and harms is uncertain *and* when significant values for the patient are at stake (as they are, for example, when termination of pregnancy for an anomalous pregnancy is a possibility), it is reasonable in clinical practice to employ respect for the autonomy of the patient as the deciding ethical principle. Moreover, doing so positively enhances the autonomy of the pregnant woman. Our approach is thus immune to the *reductio ad absurdum* that Ewigman et al. allege, because we are not defending the application of respect to autonomy to decide the use of medical interventions of "uncertain value" but only to decide the use of medical interventions for which there is no decisive beneficence-based balancing of benefits and harms but for which benefits of *certain* value exist. It cannot be emphasized enough that ultrasonographic detection of many fetal anomalies at an early gestational age to offer pregnancy management options is a certain, not an uncertain, value at this time.[1, 2] PICS thus escapes the brunt of the most powerful criticism that Ewigman et al. advance against it.

By opposing PICS Ewigman et al. are in effect advocating withholding from pregnant women information about this *certain* value of routine utlrasonography, a troubling form of paternalism. We strongly advocate that pregnant women now, not at some point in the future, be given this and other pertinent information so that they can undertake their own balancing of the certain value and the uncertainties of routine ultrasonography.

Fourth, Ewigman et al. are correct that accuracy in ultrasonography is a crucial consideration, but this is already the case. This is because of the increasingly widespread use of ultrasonography in obstetrics, quite independently of whether PICS succeeds in becoming a standard of care. The ethical issues here can be succinctly stated: (1) only individuals qualified to perform ultrasonographic examinations should perform them; (2) the informed consent process should include information about the possibility of false-negative and false-positive diagnoses, even when ultrasonography is performed by a competent examiner and interpreter. Both points simply underscore what we stated in our article defending PICS.

Finally, the correspondents criticize us for claiming that there will be an "absence of conclusive scientific data . . . in the foreseeable future" because the RADIUS trial is "attempting to produce conclusive scientific data on the value of routine ultrasonography." Dr. Ewigman kindly provided us with a copy of the RADIUS protocol, and our study of it indicates that the primary research questions of the study concern perinatal mortality and morbidity, with maternal morbidity and the diagnostic accuracy of ultrasonography among the secondary research questions. It is hoped that RADIUS will yield conclusive (i.e., unambiguous) data on its research questions, an unusual occurrence in clinical trials. Even if it were to do so, RADIUS would not totally settle the beneficence-based balancing of benefits and risks because considerations of perinatal outcome and maternal morbidity are not the entire beneficence-related story. For example, fears of unknown harms and benefits of reassuring examinations are significant beneficence-based factors, even if they are difficult to quantify.

It is hoped that one result of RADIUS will be to put the beneficence-based calculus on more reliable grounds. RADIUS is thus best viewed as permitting PICS to be enriched by information of scientific reliability about perinatal and maternal outcomes, thereby replacing less reliable information about these outcomes. RADIUS is not designed to show that the broader beneficence-based balancing of benefits and risks can be conclusively settled one way or another. There will therefore remain a decisive role for the exercise of the pregnant woman's autonomy to determine the balance that is most consistent with her values for her pregnancy. In summary, PICS should be the standard of care for the routine use of obstetric ultrasonography. The data obtained from the RADIUS project will enhance, not replace, this concept.

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Amnioinfusion and prevention of meconium aspiration syndrome

To the Editors: The article by Sadovsky et al. (Prophylactic amnioinfusion during labor complicated by meconium: A preliminary report. (AM J OBSTET GYNECOL 1989;161:613-7) raises several interesting issues. The incidence of low Apgar scores at 1 minute and 5 minutes did not differ between the amnioinfusion and control groups. A possible explanation for the reduction in need for positive pressure ventilation at birth in the amnioinfusion group is a reduction of the amount of meconium that infants aspirated before delivery. This reduction could have been achieved by diluting thick meconium in the infused normal saline solution. It is also interesting that 29% of the infants in the control group had meconium below their vocal cords despite appropriate suctioning of their oronasopharynx before delivery of the chest, as described by Carson et al.[1] I reported[2] that timing of obstetric DeLee suctioning (whether before or after delivery of the chest) did not influence the presence of meconium below the vocal cords (37% versus 36%, respectively). Using the same approach, Dooley et al.[3] reported a 19% rate of meconium below vocal cords. In this study there was a lack of correlation between variable decelerations and pres-

ence of meconium below vocal cords. It is therefore exciting to me that the rate of meconium below vocal cords could be reduced to 0% by the combination of amnioinfusion and DeLee airway suctioning. These findings truly support the hypothesis that the majority of the cases of meconium aspiration occur "in utero" and before the first breath. If this is the case then meconium aspiration syndrome is as difficult to prevent as fetal distress. Yeomans et al.[4] found that meconium-stained amniotic fluid correlates poorly with the infant's condition at birth as reflected by umbilical cord pH. The "bottom line" is that when a case of meconium-stained amniotic fluid is encountered, the current state of the art does not allow us to predict which infants will develop meconium aspiration syndrome.

In this stagnated research field of meconium aspiration syndrome, amnioinfusion offers hope. We agree with the authors that the true test will come when amnioinfusion is proved to reduce the rate of symptomatic meconium aspiration syndrome. Hypothetically, if these findings were corroborated by other investigators with a larger sample of patients, then further questions remain. (1) How aggressive will we need to be in detecting the presence of meconium in the absence of labor and intact membranes? (2) Should we use the technique of amnioscopy in patients at high risk for meconium-stained amniotic fluid? (3) How soon should amnioinfusion be started after meconium is detected into the amniotic fluid? And finally (4) will amnioinfusion affect the outcome of infants who already had meconium below vocal cords at the beginning of the procedure?

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Reply

To the Editors: We thank Dr. Falciglia for his important comments. Indeed, once the amniotic fluid is stained with meconium, aspiration can occur antepartum, intrapartum, or during the infant's first few breaths after delivery. Only the effect of the latter mechanism can be ameliorated by DeLee suctioning as described by Carson et al.[1] Amnioinfusion may decrease the risk of intrapartum aspiration, but will not prevent aspiration that occurred before labor or before the start of the amnioinfusion. We believe that by utilizing this technique further observations may help identify those fetuses who have aspirated meconium before amnioinfusion.

We concur with Dr. Falciglia that certain questions remain unanswered. The appropriate role of prenatal diagnosis of meconium-stained amniotic fluid is yet undetermined. To optimize the efficacy of amnioinfusion, it should be initiated as soon as possible after the intrapartum diagnosis of the presence of meconium. We agree with Dr. Falciglia that a larger sample of patients is needed to confirm our findings.

Although we think that intrapartum amnioinfusion has the potential to decrease the risk of meconium aspiration, this technique should not be regarded as standard obstetric care by the medical community at large until further research demonstrates the safety of this procedure.

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Use of serial human chorionic gonadotropin measurements to differentiate between intrauterine and ectopic pregnancies

To the Editors: I read the article by Lindblom et al. (Lindblom B, Hahlin M, Sjöblom P. Serial human chorionic gonadotropin determinations by fluoroimmunoassay for differentiation between intrauterine and ectopic gestation. Am J Obstet Gynecol 1989;161:397) with some bemusement. My colleagues and I showed almost 10 years ago that when serial human chorionic gonadotropin (hCG) monitoring was restricted to a group of patients roughly similar to that studied by Lindblom et al. (our patients were symptomatic whereas those of Lindblom et al. were not) the slope of the log hCG-time regression line provided a useful method of differentiating between symptomatic intrauterine and ectopic pregnancies when other tests, such as ultrasonography and culdocentesis, were nondiagnostic. We estimated the 15th percentile of the distribution of the slope of this regression line to be 0.25 among women with symptomatic but viable intrauterine pregnancies (when natural logarithms were used), and found that the value for the slope was less than this in 87% of women with ectopic pregnancies.[1]

It is salutory to note (although Lindblom et al. failed to point this out) how well these authors' findings agree with our original results, especially because they excluded patients with falling serum hCG values. By our criterion, 17/19 (89%) of their patients with ectopic pregnancies were identified as abnormal, and the false-positive rate was 18% or 27%, depending on whether one wishes to classify cases 23 and 31 (slopes, 0.248) as normal or abnormal. In either event, the difference between these values and our original figures is easily accounted for by sampling variation.

Since our early publications, Pittaway et al.[2] have questioned whether the rate of increase in hCG during the first 6 weeks of pregnancy is truly exponential as it was originally shown to be by Marshall et al.[3] However, Daya[4] and Fritz and Guo[5] have since resolved this question by showing that the log hCG-time relationship is adequately represented by a linear regression line when hCG values are <10,000 mIU/ml (international reference preparation) and <6500 mIU/ml (second international standard), respectively. In short, during the period of gestation in which Lindblom et al. obtained their data, hCG levels increase exponentially.

In an effort to improve the discrimination between normal and ectopic pregnancies, Lindblom et al. computed a number of statistics that are either statistically invalid or involve assumptions about the log hCG-time relationship in early pregnancy that are known to be untrue. What they term the *absolute slope* (final hCG − initial hCG/sampling interval) is nothing more than the slope of the linear regression of hCG (as opposed to log hCG) on time, which does not correspond with the known way in which hCG increases during the period in pregnancy studied by these authors. Their *relative slope* final hCG − initial hCG/initial hCG × sampling interval) also does not correspond with any known probability model for the hCG-time relationship in early pregnancy because it is assumed in the computation that the proportion by which hCG increases per day is constant. This assumption has not been validated by the authors, nor does it accord with what would be predicted by an exponential (or, for that matter, a quadratic) log hCG-time relationship. The *relative slope* obtained under an exponential model would in fact depend on what sampling interval was used. For example, if the initial hCG is 500 and the doubling time is constant and equal to 2 days, the value obtained for the relative slope would be 0.41, 0.5, 0.61, 0.75, and 0.93, respectively, for sampling intervals of 1, 2, 3, 4, and 5 days.

However, the most questionable aspect of the authors' analysis is the one they recommend for clinical use, namely, the putative regression relationship between the absolute slope and the initial hCG value, which the authors claimed allows better discrimination between ectopic and normal intrauterine pregnancies. But, because the initial hCG value features in both the independent and the dependent variable, a spurious dependency between the two variables is introduced that invalidates the analysis. This is easily illustrated by calculation of the absolute slope for identical proportionate increases in the serum hCG at two different initial hCG values. Suppose that the serum hCG increases by 80% over a 2-day period. If the initial hCG is 200 mIU/ml this would yield an absolute slope of 80, but if the initial hCG value is 2000 mIU/ml, the absolute slope would be 800. It is easy to see that the slope would increase with initial hCG even if the rate of increase was exponential.

There are other unsatisfactory aspects of the analysis, the most notable of which is that prediction intervals were not constructed around "the discriminatory curve . . .between the two clusters of data points." Without these, it is not possible to predict how well this discriminatory curve would perform in other samples from the same population. Inasmuch as many of the data points lie close to the curve, it is more than likely that the discrimination achieved in the authors' sample of patients would not be reproduced in further sets of data.

To provide a heuristic test of the authors' approach, the absolute slope was calculated for the data previously published by Kadar and Romero.[6] For each patient, it was determined whether the absolute slope predicted from the equation derived by Lindblom et al. ($y = 12.31 \cdot x^{0.46}$) was greater or less than the observed absolute slope. The hCG score proved to be abnormally low in 25/34 (74%) of our ectopic pregnancies and to be normal in 38/41 (93%) of normal pregnancies. The specificity of our criterion was 37/41 (90%) and the sensitivity was 27/34 (80%).

These findings show a very important principle of medical testing. If one is trying to distinguish between two groups of persons by means of a test and values among the two groups overlap, it is not possible to improve the test's performance by changing the critical value of the test because test performance is solely dependent on the degree of overlap. Inasmuch as the rate of hCG increase in serum among women with ectopic and intrauterine pregnancies overlaps, one can predict that attempts to improve the effectiveness of serial hCG testing as a means to distinguish between these two conditions that consist simply of changing the test criterion (whether arrived at by legitimate or illegitimate statistical means or arbitrarily) are inevitably doomed to failure.

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Reply

To the Editors: We are honored by Dr. Kadar's attention to our article and we have tried to extract the main points in his criticism. Thus, according to Dr. Kadar, our article has the following shortcomings: (1) we failed to point out the similarity between our results obtained with the human chorionic gonadotropin (hCG) score

and those obtained by Kadar et al. in 1981[1]; (2) we assumed that the hCG-time relationship is linear; (3) we did not provide prediction intervals for our discriminatory curve; (4) we applied regression analysis improperly—". . . a spurious dependency between the two variables . . ."; and (5) the good performance of the hCG score was caused purely by chance— ". . . it is more than likely that the discrimination achieved in the authors' sample of patients would not be reproduced in further sets of data."

In reply to this criticism we have the following comments.

The performance of any diagnostic test is highly dependent on the patient material to which it is applied. In the article by Kadar et al.[1] no precise information about selection criteria was provided. Although Dr. Kadar states in his letter that their and our patient groups were "roughly similar," we had no basis for such an assumption. During the past decade Dr. Kadar's group has published >10 papers concerning their approach for analysis of hCG patterns in early pregnancy and their concept of a discriminatory hCG zone. Of all these publications we referred to the one that we considered most readable and relevant.[2]

We explicitly stated that we consider the hCG-time relationship as being nonlinear in viable intrauterine pregnancy. However, *to simplify calculations* we approximated this relationship to be linear over a period of up to 6 days. By use of a sampling interval of 1 to 2 days this error is reduced. Regardless of the mathematic function used to describe the normal increase of hCG in serum in viable intrauterine pregnancies, there is a difference between pathologic and normal pregnancies with regard to the rate of increase in serum hCG, and this difference can be analyzed for differential diagnostic purposes. Because the fitting of mathematic functions to biologic data are always approximations, we believe that there is no single true way to describe the course of a biologic event, such as the hCG increase in early pregnancy. The clinical usefulness of a diagnostic test is determined not only by its validity and pure scientific qualities, but also by its ease of use. Whereas the standards with regard to the former properties must always be high, it is equally important that descriptions and explanations of the tests are intelligible. Otherwise, an original work runs the risk of not being properly cited and the ideas advanced may not be put to use. The following passage cited from Kadar et al.[1] serves to illustrate difficulties of this kind:

Dividing the specificity (86%) by the false-negative rate (13.3%) and multiplying the result (6%) by the intrauterine:ectopic pregnancy incidence ratio enables one to calculate the number intrauterine pregnancies correctly diagnosed for every patient with ectopic pregnancy in whom the diagnosis is delayed beyond 48 hours.

A nomogram is what is needed to use the hCG score. In contrast, to use Dr. Kadar's method one would need a scientific calculator or log tables.

It is true that we have not provided prediction intervals for the discriminatory curve. The validity of the diagnostic test is currently being evaluated in a prospective study of a large patient material. So far, the validity of the test has not declined.

Table I. Results for pathologic pregnancy

	Sensitivity	*Specificity*
Kadar's method	0.89	0.90
hCG score	0.89	0.95

We agree that the initial hCG value features both in the independent and the dependent variable. We disagree with Dr. Kadar's contention that this introduces a spurious dependency. It is obvious that the relationship between daily change and the initial hCG value seen in ectopic pregnancies is different from that seen in viable intrauterine pregnancies. Use of the initial hCG as an independent variable in the prediction of the change in hCG is a permitted method no different from predicting sick leave of a population in 1989 with the use of sick leave in 1988 in the same population as an independent variable.

We compared the performance of the hCG score against that of Kadar's method in our updated material of 160 ectopic pregnancies and 73 viable intrauterine pregnancies. Results we obtained for pathologic pregnancy are shown in Table I. From these results we conclude that in early pregnant patients (hCG <4000 IU/L), the hCG score performs as well as (or even better than) the method of Kadar et al. Inasmuch as the hCG score also is much easier to use, we believe that it constitutes an important improvement in terms of clinical usefulness.

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Intracellular sodium levels in pregnant women with hypertension

To the Editors: I am surprised that Sowers and colleagues (Sowers JR, Zemel MB, Poronsteen RA, et al. Erythrocyte cation metabolism in preeclampsia. Am J Obstet Gynecol 1989;161:441-5) placed so much emphasis in their discussion on a laboratory value (parathyroid hormone) that was not significantly different from that of controls.

Besides, in contrast to the authors' negative findings, Tranquilli et al.[1] found an increase in intracellular sodium in pregnant women with hypertension. Even Weissberg et al.[2] whom the authors use as support for their negative findings, suggest that a negative finding "does not rule out the possiblity that subjects within the group might not have important increases in intracel

lular sodium over the course of their pregnancy." Given that the authors found elevated levels of endoxin in the hypertensive group, it would be interesting to learn the intracellular values of sodium in subjects with significantly elevated endoxin values.

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Reply

To the Editors: Although increased circulating endoxin may be expected to inhibit sodium-potassium adenosine triphosphatase activity and thereby reduce intracellular sodium levels, our data do not support this. However, our findings are consistent with a previous report that *chronic* exposure to digoxin does not result in reduced sodium pump activity or increased intracellular sodium levels, although short-term treatment does result in these effects.[1]

In addition, we found that both plasma endoxin and erythrocyte sodium-potassium adenosine triphosphatase activity exhibit significant increases during pregnancy.[2] Further, there is a significant positive correlation between the two ($r = 0.72$) rather than the expected inverse relationship, suggesting that the sodium-potassium adenosine triphosphatase exhibits an adaptive response to the high endoxin levels.[2] Thus, these data further support the finding that increased endoxin levels in patients with preeclampsia does not result in a chronic suppression of sodium-potassium adenosine triphosphatase activity and thereby an increase in intracellular sodium levels.

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Screening infertile women for subclinical hypothyroidism

To the Editors: Wilansky and Greisman reported an association between menorrhagia and an abnormal thyroliberin (thyrotropin releasing hormone) stimulation test (Wilansky DL, Greisman B. Early hypothyroidism in patients with menorrhagia. Am J Obstet Gynecol

sulted in elimination of menorrhagia. Bohnet et al.[1] reported that subclinical hypothyroidism was found in 20 of 150 infertile women with anovulation or luteal insufficiency. Thus, it is common practice to screen infertile women with the use of thyroid function tests (thyroxine, thyrotropin, triiodothyronine resin uptake, and free thyroxine index).

However, a cursory review of thyroid function test results of infertile women at our institution suggested a low prevalence of abnormal thyroid function test results from such screening. Therefore, we performed a survey to determine the prevalence of subclinical hypothyroidism in a population of infertile women and to ascertain whether routine screening of this population for subclinical hypothyroidism with thyroid function tests, especially thyrotropin measurement, is justified.

We reviewed the records of 210 patients enrolled in our infertility clinic during a 1-year period. None of these patients had clinical or laboratory findings consistent with the presence of overt thyroid disease, thyroid enlargement, or thyroid autoantibodies. We categorized our patients' infertility according to standard clinical criteria. Ovulatory dysfunction was suspected from a clinical history of amenorrhea or irregular menses. This diagnosis was confirmed if the basal body temperature showed a prolonged (≥21 days) follicular phase or a monophasic pattern accompanied by a decreased (<3 ng/ml) serum progesterone concentration or if an endometrial biopsy specimen showed proliferative endometrium. A luteal phase defect was not considered an ovulatory disorder.

Serum from all patients' blood samples were assayed for thyroxine and thyrotropin ("regular" immunoradiometric assay) in the automated radioimmunoassay—high technology instrument (Becton Dickinson Immunodiagnostics, Salt Lake City, Utah).[2] The triiodothyronine resin uptake assay (Nuclear Diagnostics, Troy, Mich.) was performed on all samples and the results were used to calculate the FTI = (thyroxine) × [T_3(RU)/30], where FTI = free thyroxine index, T_3 = triiodothyronine, and RU = resin uptake. Prolactin concentration was determined with the Tandem-R prolactin kit (Hybritech Inc., San Diego, Calif.).

Patients ($n = 8$) with subclinical hypothyroidism were asymptomatic but had an increased thyrotropin concentration (mean thyrotropin ± SD = 8.3 ± 2.7 mIU/L; range, 5.3 mIU/L to 12.3 mIU/L) and thyroxine, triiodothyronine resin uptake, and free thyroxine index values within the normal reference range for these analytes established in our laboratory. It has been previously shown that an increased (5.2 mIU/L < [thyrotropin] < 10.4 mIU/L) thyrotropin concentration in euthyroxinemic patients is commonly associated with abnormal thyrotropin-releasing hormone test results suggestive of subclinical hypothyroidism.[3] At a thyrotropin cutoff value of 5.2 mIU/L (i.e., the upper limit of the normal reference range for thyrotropin concentration established in our laboratory), diagnostic sensitivity and specificity were 71% and 96%, respectively.

(87%) patients with an increased thyrotropin concentration and in 55 of the remaining 202 (27%) women who had a normal thyrotropin concentration. By χ^2 analysis, these distributions were significantly different ($p < 0.001$). Conversely, the incidence of subclinical hypothyroidism in dysovulatory women ($n = 62$; seven with an increased thyrotropin concentration and 55 with a normal thyrotropin concentration) was 11.3%. Prolactin concentrations were normal (mean prolactin ± SD = 6.6 ± 2.3 ng/ml; normal range, 0 ng/ml to 20 ng/ml) in serum samples from all eight patients who had an increased thyrotropin concentration.

Patients with subclinical hypothyroidism are generally asymptomatic and produce suboptimal levels of thyroid hormones that are compensated for by increased output of thyrotropin to maintain euthyroxinemia.[4] This disorder has been estimated to occur in up to 7% of the adult population[5] and is generally considered an innocuous disease, although it has been linked to hypercholesterolemia and impaired cardiac systolic time intervals.[3] In our population of infertile women the incidence of subclinical hypothyroidism was only 3.8%, but in the subset of women with ovulatory dysfunction the incidence increased threefold to 11.3%.

If the diagnostic sensitivity and specificity of a test and the prevalence of disease in a population are known, the positive or negative predictive value of this test can be calculated.[6] With the use of the sensitivity (71%) and specificity (96%) of the thyrotropin test (at a thyrotropin cutoff concentration of 5.2 mIU/L) to predict subclinical hypothyroidism and the prevalence (3.8%) of this disease in our population of infertile women, the positive predictive value is only 41% (i.e., 59% of all patients with an increased thyrotropin concentration will not have subclinical hypothyroidism). However, among dysovulatory women the positive predictive value of the thyrotropin test increased to 68%.

We conclude that in a population of infertile women, subclinical hypothyroidism may be observed occasionally; however, the prevalence of this disease in this group of women is probably no greater than the prevalence in the general population. Even if the diagnostic sensitivity and specificity of the thyrotropin test were increased by use of currently available "sensitive" thyrotropin assays,[2] the low prevalence of subclinical hypothyroidism in infertile women suggests that it may not be cost effective to routinely screen this group of women for this disease. However, in our population of dysovulatory women the prevalence of subclinical hypothyroidism increased threefold. Wilansky and Greisman have proposed "systematic study of thyroid function" in women with menorrhagia. Similarly, our data suggest that it may be prudent to screen dysovulatory women for subclinical hypothyroidism with a thyrotropin measurement.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.

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Reply

To the Editors: We thank Dr. Strickland and colleagues for sharing with us their important and significant observation on subclinical hypothyroidism in persons with infertility, and in particular those with ovulatory dysfunction. We were particularly interested to be informed of the 11% prevalence of hypothyroidism in the ovulatory dysfunctional group and the suggestion to screen dysovulatory women for subclinical hypothyroidism. I wonder whether Dr. Strickland and colleagues have had an opportunity to note the response to L-thyroxine administration in these dysovulatory patients with subclinical hypothyroidism.

The endocrine literature has characterized subclinical hypothyroidism as occurring in two phases. The later phase is that in which there is random thyrotropin elevation. The earlier phase is identified only after administration of thyrotropin-releasing hormone. We showed that whereas within the normal reference range serum thyroxine levels are significantly lower in the early phase than in a control population. If Dr. Strickland's group wished to maximize their recognition of subclinical hypothyroidism a modified thyrotropin-releasing hormone test might be desirable. In some persons with subclinical hypothyroidism, the diagnosis will be missed because the random thyrotropin elevation in early hypothyroid states may be intermittent, similar to the gonadotropic hormone elevation in early ovarian failure.

Finally, because we are talking about clinical manifestation of so-called *subclinical hypothyroidism,* we wonder whether this term continues to be appropriate. We have suggested the term *early hypothyroidism* to replace such terms as triiodothyronine euthyroidism, *compensated hypothyroidism,* and *subclinical hypothyroidism.* Furthermore, we believe that this term may stimulate efforts to clarify the clinical significance of these important phases of developing hypothyroidism.

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Study results vary in count-to-10 method of fetal movement screening

To the Editors: We read with interest the article by Moore and Piacquadio (Moore TR, Piacquadio K. A prospective evaluation of fetal movement screening to reduce the incidence of antepartum fetal death. AM J OBSTET GYNECOL 1989;160:1075-80) that concluded that the "Cardiff count-to-10" method of fetal movement screening reduces the prevalence of antepartum fetal death. We recently reported a very large randomized controlled trial[1] that came to the opposite conclusion. There may be a number of reasons for this discrepancy.

It is possible that Moore and Piacquadio's finding may be explained by problems that resulted from imprecision and bias. Their sample size is very small (about 4000 compared with 68,000 in our study). Small trials tend not only to miss finding true effects, but also to overestimate the size of any effect found. (In fact, at a very early stage of our trial, the distribution of antepartum deaths between the counting and control groups looked very similar to that of a small randomized controlled trial by Neldam.[2]) The fact that in Moore and Piacquadio's study the death rate was higher than that expected in the control period and was so much lower during the study period suggests that the pattern may well be a result of random variation over a very short time period, rather than being a true effect of the policy.

The second potential problem is one that arises from bias. The most serious component of this is selection bias. The concern must be that as control and study groups were neither randomized nor contemporaneous, they might differ from each other in respects other than participation in the counting policy. Could the authors reassure readers of the comparability of the groups? Another source of selection bias is that that occurs because of selective withdrawals from the cohorts before the analysis. The fact that the numbers of women in the two 7-month time periods are so different (2519 and 1864) suggests that this may have happened. Was the study group based on "compliers" only? This could give a false picture of the effects of the policy because compliers tend to do better than noncompliers, regardless of whether the management with which they are complying is effective.[3]

The third potential source of bias is that at case ascertainment. Were decisions about the timing of death (i.e., whether the death occurred before or after the onset of labor, or at what gestational age) and about the cause of death made without knowledge of whether the women had their antenatal care in the study or control time period?

Apart from these issues of imprecision and bias, it is possible that special aspects of Moore and Piacquadio's counting protocol may go some way toward explaining their findings. This protocol was applied in the evenings, and their pilot study found that women counted to 10 movements in a very short time (mean 20.9 minutes). This is very much quicker than has been reported elsewhere in the literature.[4] Probably because of this, their rate of compliance was also very much higher than in other studies.

Moore and Piacquadio's replies to these concerns (particularly about bias) may help readers to interpret the study's findings.

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Reply

To the Editors: We thank Drs. Elbourne and Grant for their interest in our recent study. We also read with interest the results of a large-scale randomized control trial that came to the opposite conclusion of our study.[1]

With regard to the question of sample size and study precision, we used a χ^2 comparison to contrast the number of deaths that occurred in the control period as compared with that in the study period. As noted in the article, this was statistically significant at the 99% confidence level. We are now able to report a 30-month update in our study, which comprises 5758 patients managed with a count-to-10 method with the use of a 2-hour limit. During this period there have been 21 stillbirths in 5758 births for a fetal mortality rate of 3.6 per 1000. This is still significantly less than the fetal mortality rate in the control period, and indeed approximately half of the fetal mortality rate in the state of California. One of the problems with the study of Grant et al.[1] is that the baseline fetal mortality rate was only 2.67 per 1000. These rates have not been achieved in the United States and may partially explain why the large-scale study failed to show a significant effect.

With regard to the comparability of the groups in the control study period, Naval Hospital San Diego has served the same military dependent population over the past two decades. Demographic surveys during this period have failed to show any drift in the basic obstetric indicators of this population. Moreover, we statistically analyzed all fetal deaths that occurred during our study. Two of the four mortalities occurred before 28 weeks' gestation, one in a patient with no prenatal

care and one in an anencephalic fetus. All deliveries of ≥20 weeks' gestation were used in the denominator.

The study of fetal movement counting with contemporaneous groups is extremely difficult because of the problem of "bleedover." This was addressed in the study of Grant et al.[1] by use of the cluster technique. In our particular patient population, a control group could not be identified that would not have gained access to and readily accepted fetal movement counting practices. Nevertheless, we strongly believe that a fetal mortality rate of 3.6 per 1000 is an enviable rate among middle-class women in the United States.

In our opinion, the largest difference between the study of Grant et al.[1] and ours is the rate of compliance. As documented in our article, 10 fetal movements in the evening are counted within 10 to 15 minutes by most women. Rapid test completion has likely been the major factor responsible for continued high compliance in our population (>93% during the past 30 months). Our study placed value on a sensitive movement alarm signal, whereas the study of Grant[1] chose specificity; unfortunately, this resulted in a significant proportion of patients with decreased fetal movement seen after fetal death.

We believe that an appropriately designed fetal movement criterion should be highly sensitive and identify fetuses at risk that need traditional antepartum testing. Given the marked differences in the two methods, a large-scale, controlled, randomized study of the San Diego count-to-10 method is indicated.

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Changes in the incidence of ectopic pregnancy in Hungary

To the Editors: I have read with great interest the recent work of Mäkinen et al. (Mäkinen JI, Erkkola RU, Laippala PJ. Causes of the increase in the incidence of ectopic pregnancy. A study on 1017 patients from 1966 to 1985 in Turku, Finland. Am J Obstet Gynecol 1989;160:642-6), giving account of a more than threefold increase in the rate of ectopic pregnancies in Finland between 1966 and 1985. Their data appear to indicate that the increase of extrauterine gestation has reached epidemic proportions in that country. Noting that Fins and Hungarians, living under markedly different geographic and climatic conditions, both belong to the Finn-Ugor racial group, we thought that it was matter of interest to investigate the changing patterns of the incidence of ectopic pregnancy in our country during the last half a century.

We are inclined to identify three important periods of time in the context of the relevant data. The years of 1946 to 1950 marked the beginning of the use of antibiotics in Hungary. At that time sophisticated contraceptive techniques were not as yet available. During the years of 1964 to 1968 advanced birth control methods were known in Hungary but were not yet used widely in the population. By the years of 1984 to 1988, hormonal contraceptive methods were extensively used and so were virtually all broad-spectrum antibiotics. We found it necessary to use the above yardstick for the evaluation of our data, noting the fact that contemporary treatment of pelvic inflammatory conditions and the use of oral contraception are generally considered significant with regard to the etiology of ectopic gestation.

The rate of ectopic pregnancy in Hungary during the above quoted 5-year periods ranged between 0.45% and 0.54% (Table I). The increase from 450 ectopic pregnancies per 100,000 total pregnancies in 1964 to 1968 to 540 in 1984 to 1988 is significant at the $p < 0.005$ level. The 480 extrauterine pregnancies per 100,000 total gestations in the years of 1946 to 1950 is not significantly less than that noted in 1984 to 1988. (The χ^2 test was used for determining the level of significance.) The difference between the 1946 to 1950 and the 1964 to 1968 rates is negligible. However, the increase by 1984 to 1988 is at the range of 20%. Our data appear to indicate that the increase of the rate of ectopic pregnancy in Hungary was markedly less than that observed in northern Europe and the United States.[1-3]

Table I. Rate of ectopic pregnancies, in comparison with all pregnancies, in course of three separate 5-year periods in Hungary

First 5 yr		*Second 5 yr*		*Third 5 yr*	
yr	*%*	*yr*	*%*	*yr*	*%*
1946	0.36	1964	0.5	1984	0.5
1947	0.39	1965	0.48	1985	0.54
1948	0.5	1966	0.44	1986	0.58
1949	0.55	1967	0.43	1987	0.52
1950	0.6	1968	0.38	1988	0.56
Mean	0.48		0.45		0.54

The cause of the increase in the incidence of ectopic pregnancy is multifactorial. A discussion of the hypothetical explanations for the difference between the observed increase in the rate of ectopic pregnancy between Hungary and Finland is beyond the scope of this short communication.

I thank András Klinger, PhD, Central Statistical Office, Budapest, for his valuable help.

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Reply

To the Editors: We thank Dr. Jakobovits for the interest concerning our article.

In his letter Dr. Jakobovits has shown a negligible increase in the rate of ectopic pregnancy in Hungary, which is in opposition to the great increase of ectopic pregnancy in many countries in western Europe and in the United States. He did not endeavor to hypothesize the reasons for this difference, and we do agree that this may turn out to be somewhat difficult. However, at least two obvious differences between Hungary and Finland should be pointed out. First, although the exact figures for Hungary are not available to us, the use of an intrauterine contraceptive device has probably been much more limited in Hungary than in Finland, especially in the 1970s and early 1980s. This could be considered as an additional, yet indirect evidence for the role of the intrauterine contraceptive device in the increase in the rate of ectopic pregnancy. Second, the effect of improved diagnosis also needs consideration. In Finland this may explain some of the increase in the rate of ectopic pregnancy, but to be able to compare Hungary and Finland in this regard, we must know the workup used in Hungary for the diagnosis of ectopic pregnancy in the years of the study, e.g., how widespread the use of highly sensitive pregnancy tests, ultrasonography, and laparoscopy has been.

Incidentally, an interesting observation on the relation between legal abortion and ectopic pregnancy may be made when one is looking at the statistics from Hungary and Finland. The rates of legal abortion in Hungary have been more than fivefold those in Finland. In our study legal abortions did not show any strong association with the increase of the rate of ectopic pregnancy. The comparison of figures from Hungary and Finland again gives indirect support to this observation.

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Cerebral palsy and intrapartum fetal acidemia

To the Editors: I believe that the data of Dennis et al. do not warrant the author's conclusions (Dennis J, Johnson A, Nutch L, Yudkin P, Johnson P. Acid-base status at birth and neurodevelopmental outcome at four and one-half years. AM J OBSTET GYNECOL 1989;161:213-20).

Just as Baird's documentation of the interacting social factors that influence health and child-bearing failed to be accepted in America,[1] to speak of "impairment codes" does not have current American obstetric clinical or medical-legal implications. The present issue on this side of the Atlantic is cerebral palsy and its possible relationship to intrapartum fetal acidemia. The authors started with a data base of 1210 cases at term, which should have produced at the most only two cases of cerebral palsy. If only 10% to 20% of cases of cerebral palsy are due to intrapartum fetal distress, I believe the authors whould have to have had access to at least 5000 cases to have one case of cerebral palsy caused by obstetric events. Furthermore, no information is given about genetic factors, which may have a significant role in developmental "impairment."

While the authors spoke of "physiologic acidosis," no mention was made of lactic acid in their discussion. Hendricks[2] noted that fetal difficulty occurred more frequently when maternal lactic acid values failed to increase near term. The literature on lactic acid as a fetal substrate is extensive.[3] Presumably, its production by the placenta has fetal benefits, although it may at the same time contribute to the apparent acidemia of the fetus.[4] Nevertheless, such a metabolic acidemia would not be "physiologic" in that it is highly variable.

Years ago, Kaiser and I[5] showed that altering maternal pH likewise altered fetal pH. In any population of newborns, to attempt to discuss the significance of fetal acidosis in the absence of maternal pH determinations is in my opinion futile.

I continue to believe that the possible role of fetal acidemia will be delineated only when routine maternal and umbilical pH values are obtained on thousands of deliveries. Then, when cases of cerebral palsy occur,

we can accurately determine the significance (if any) of "fetal acidosis."

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Reply

To the Editors: We find it difficult to relate the comments in the first part of Dr. Goodlin's letter to our own particular study. Our study was designed to find out whether acid-base status at birth in term infants would be predictive of neurodevelopmental outcome at age 4 to 5 years. The outcome we were concerned with was not primarily cerebral palsy; rather it was the relatively large proportion of children (10% to 20%) with disability caused by subtle neurodevelopmental impairment. As Dr. Goodlin correctly points out, cerebral palsy is a relatively rare condition. Had we wished to study the possible association of acid-base status at birth and cerebral palsy, we would not have chosen a cohort design.

We used as outcome measures a wide range of standardized developmental tests. Dr. Goodlin suggests that results of such tests carry no clinical or medicolegal validity. On the contrary, such tests are widely used in clinical practice on both sides of the Atlantic, and our experience in the United Kingdom is that tests of this type are certainly recognized in courts of law as valid measures of neurodevelopmental status in children. We showed no association whatever between poor performance on these tests and our measure of acid-base status. The "impairment codes" that Dr. Goodlin has singled out were derived from these standardized tests and merely represent one of many attempts to ensure that we were not missing any associations in our data. We believe the conclusions we have drawn are entirely valid within the context of our study and are well supported by our data.

Dr. Goodlin, as expected, raises several pertinent issues on the question of fetal acidosis. In particular, he poses the question as to whether maternal acidosis in labor could have made a significant contribution to the fetal acidosis at birth. If so, this "apparent" fetal acidemia could not be considered physiologic. This is extremely unlikely because of several issues. In our study we were considering severe levels of fetal acidosis: a first level that produced a pH <7.12 and a second level with a pH <7.04 (mean pH for this group was 6.97). At these fetal levels the maternal contribution would be small.[1] In the original study from which our cohort was drawn, simultaneous umbilical arterial and venous measurements were made.[2] The base excess was always greater and the pH lower in the umbilical artery than in the umbilical vein. Hence we assumed the acidosis to be mainly emanating from the fetus. A further study of these paired samples demonstrated that maternal intrapartum factors as opposed to fetoplacental factors made a comparatively small contribution to fetal arterial acidosis.[3]

Hence we do not agree with Dr. Goodlin's suggestion that in the absence of measures of maternal acid-base status our umbilical arterial measures are "futile."

As to the question of the "physiologic" nature of the response, it is the production of lactic acid by the fetoplacental unit as an energy-supplying response to anaerobiosis—the very process referred to by Dr. Goodlin—that we term "physiologic."

The issue of acidosis and its relation to asphyxial injury needs urgent resolution. We believe our study is entirely valid in suggesting that a one-off measure of umbilical arterial pH and base deficit is not a good measure of fetal asphyxia, a view increasingly shared by others.[4-6]

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Spontaneous resolution of a nuchal fetal cystic hygroma diagnosed early in the second trimester of pregnancy

To the Editors: We read with interest the article by Bronshtein et al. (Bronshtein M, Rottem S, Yaffe N, Blu-



Fig. 1. Nonseptated nuchal cystic hygroma in 14-week-old fetus. *Arrow* is aimed at cystic mass.

menfeld Z. First-trimester and early second-trimester diagnosis of nuchal cystic hygroma by transvaginal sonography: Diverse prognosis of the septated from the nonseptated lesion. AM J OBSTET GYNECOL 1989; 161:78-82). The authors report on eight cases of cystic hygroma diagnosed early in the second trimester of pregnancy. In the four cases of nonseptated nuchal cysts, normal fetal karyotype was detected in amniocentesis, and in all of them spontaneous resolution of the cystic neck mass was observed on further scans. However, in the septated cystic hygromas the outcome was grave and in two cases an abnormal fetal karyotype was found.

We have recently encountered two cases of nonseptated cystic hygromas (Fig. 1) with spontaneous resolution of the sonographic signs of cystic neck mass on further scans during a few weeks. Both cases were first diagnosed at 14 weeks' gestation. In one of the fetuses genetic amniocentesis performed at 16 weeks of pregnancy revealed a normal 46,XX karyotype, and the pregnancy was allowed to continue, resulting in delivery of a normal healthy infant. However, chromosomal analysis of the second fetus revealed trisomy 18, and the pregnancy was terminated.

Our data of an unfavorable outcome in a nonseptated nuchal hygroma are in disagreement with the author's suggestion and conclusion that both types of hygromas are present: "septated lesion—bad outcome" versus "nonseptated lesion—good outcome." We agree with the authors that more data should be collected to correctly assess the fetal prognosis in cases of early detection of cystic nuchal hygromas.

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Reply

To the Editors: We have read with interest Drs. Meizner, Levy, and Cohen's letter, and we are grateful for their important contribution, which strengthens the recommendation expressed in the last paragraph of our aticle: "Until more data are collected to support the relatively good prognosis of those cases not associated with hydrops, we recommend amniocentesis for karyotyping and α-fetoprotein measurement in each case of cervical cystic hygroma."

Since the publication of our article, our series of septated and nonseptated nuchal cystic hygromas increased significantly, and it now consists of 27 cases—14 nonseptated and 13 septated cystic hygromas. Out of the 13 cases with the septated lesions, six were dyskaryotic fetuses (three trisomy 21, two trisomy 18, and one 45,XO); all of these suffered intrauterine fetal death or therapeutic abortion. Five other pregnancies in this group, whose fetal karyotype is unknown, ended in missed abortion. The last two fetuses in this group of septated hygromas were eukaryotic and were delivered at 29 and 34 weeks, respectively. However, the first of them suffered from hydrocephalus and fetal distress and died in the early neonatal period. The second was delivered at 34 weeks of gestation and developed normally afterward. Out of 13 pregnancies with septated cystic hygromas, only one generated a normal fetus, i.e., a "take-home baby" rate of 6.2%.

In the group of nonseptated cystic hygromas, out of 14 diagnosed cases, 13 were delivered as normal healthy, eukaryotic neonates, whereas the fourteenth suffered nonimmune hydrops and early neonatal death. In this group the "take-home baby" rate was 92.8%, which obviously is a significantly better outcome than that of the septated cystic hygromas.

As to the case of Drs. Meizner, Levy, and Cohen, with cystic hygroma and trisomy 18, we speculate that one may diagnose a septated lesion by looking at their figure. The arrow is indeed aimed at the cystic mass, but the white horizontal delicate line appearing in the cystic hygroma in their figure, may well represent a septum within the cytic lesion. Moreover, this picture seems to be taken from a transvaginal scan performed with a Siemens ultrasonography instrument, using a 5.0 MHz transducer. The resolution of the 5.0 MHz transducer in our experience is somewhat inferior to that of a 6.5 MHz transducer; therefore delicate septae within a cystic hygroma might not be seen with the lower frequency transducer and may be detected with the higher frequency transducer (6.5 MHz). Regardless of such a possibility, we absolutely agree with Drs. Meizner, Levy, and Cohen, that all of us must be very careful and therefore determine the karyotype in every detected cystic hygroma—septated and nonseptated. At the same time we must conclude from our enlarged series the same conclusion we reached in our article: "septated lesion—bad outcome" versus "nonseptated lesion"—relatively "good outcome." The fetal death rate was 92% (12/13) in the "septated" group versus 7% (1/14) in the "nonseptated" group, and the "take-home baby"

rate was 7.7% in the "septated" group versus 93% in the "nonseptated" group.

Again we thank Drs. Meizner, Levy, and Cohen for their important contribution and accept their conclusion that karyotype determination should be recommended in every case of diagnosed cystic hygroma—both the high-risk (septated) and the relatively low-risk (nonseptated) lesion.

Moshe Bronshstein, MD, and Zeev Blumenfeld, MD
Department of Obstetrics and Gynecology "A," Rambam Medical Center, Technion-Faculty of Medicine, Haifa, Israel 31096

Mortality rates ignore population segment

To the Editors: An article by Resnick et al. (Resnick MB, Carter RL, Ariet M, et al. Effect of birth weight, race, and sex on survival of low-birth-weight infants in neonatal intensive care. Am J Obstet Gynecol 1989; 161:184-7.) reports mortality rates among infants cared for in 10 neonatal intensive care units that constitute the State of Florida's Perinatal Intensive Care Program. These babies were born during a 7-year period. The data presented are very useful, but with one very important caveat. The authors failed to address those babies who were never transferred to the program. As a consequence, their mortality figures are applicable only to programs with referral patterns exactly like theirs.

Saigal et al.[1] illustrate the error introduced when babies born in the community but never transferred to the program are ignored. A total of 66 (12%) of 521 babies with birth weights of 500 to 1000 gm died in community hospitals. None cared for only at community hospitals survived. If these 66 babies had been ignored, mortality rates for the group would have fallen from 53% to 46%. For comparison, mortality figures for live born infants from an inborn population that is approximately 65% black and 80% insured by a third party (private insurance, health maintenance organization, or Medicaid) born during the period July 1987 to December 1988 is provided by birth weight and gestational age in Table I. Provision of data by gestational age is less exact than by birth weight, but is inherently more useful to the obstetrician, and perhaps is as accurate with modern obstetric practice as is prenatal estimate of weight.

Table I. Mortality rates by birth weight and gestation

	*No.**	*Survival (%)**
Birth weight (gm)		
<501	9	0.0
501-600	17	5.9
601-700	11	54.5
701-800	16	56.2
801-900	12	100.0
901-1000	14	92.9
Gestational age (wk)		
<23	15	0.0
23	9	11.1
24	11	27.3
25	15	73.3
26	20	80.0
27	10	80.0
28	16	100.0

*Babies born in hospital July 1987 to December 1988; survival to discharge from hospital.

Although the point estimates of survival rates by birth weight are useful, the utility could be enhanced by the 95% confidence limits of survival rates. Variation by year or by hospital could be used to determine the variability in the estimate. The clinician could then more accurately convey the uncertainty of survival in these small infants.

Kenneth L. Harkavy, MD
Division of Neonatology, Columbia Hospital for Women Medical Center, 2425 L St. N.W., Washington, DC 20037

REFERENCE

1. Saigal S, Rosenbaum P, Hattersley B, Milner R. Decreased disability rate among 3-year-old survivors weighing 501 to 1000 grams at birth and born to residents of a geographically defined region from 1981 to 1984 compared with 1977 to 1980. J Pediatr 1989;114:839-46.

Reply

To the Editors: We appreciate the opportunity to respond to the three points raised by Dr. Harkavy in his Letter to the Editors.

In our sample of >16,000 neonates who received neonatal intensive care unit care in Florida's 10 Regional Perinatal Intensive Care Centers, we found no significant differences between survival of inborn neonates and that of neonates transferred from other hospitals. Data from the State of Florida indicate that the vast majority of high-risk infants in the 10 catchment areas were transferred to one of our centers for neonatal intensive care unit care. If the severity of illness in the transferred group differed from that of the inborn group, the survival rates should have been different. They were not.

Whereas gestational age is widely used by obstetricians as an indicator of prematurity, it is quite inexact for infants of extremely low birth weight (<1000 gm). It is hoped that research with ultrasonography in the coming decade will provide a more accurate method to evaluate the degree of prematurity.

When we analyzed our data by both race and sex, the 95% confidence level was a maximum of ±2% for neonates with birth weights of >1000 gm, ±4% for those who weighed 600 to 100 gm, and ±6% for those who weighed <600 gm. A table listing the SE for mortality in each of the 20 birth weight categories by race

and sex (from which the confidence levels were derived) may be obtained from the first author.

Michael B. Resnick, EdD

Department of Pediatrics, University of Florida College of Medicine, Gainesville, FL 32610

Mario Ariet, PhD

Department of Medicine, University of Florida College of Medicine, Gainesville, FL 32610

How sperm commence movement and their isolation for in vitro fertilization and sex selection

To the Editors: Recent observations have shown that there is no movement in a drop of just-ejaculated semen, reflecting the quiescence of sperm in vivo. Within a few minutes, the terminal filaments of the sperm tails begin to vibrate very rapidly; soon thereafter a wave of undulatory movement passes up the tail toward the midpiece, followed in short time by a vibratory movement of the head, all in situ. By the time the seminal fluid approaches normal viscosity, suddenly the sperm begin very rapid forward locomotion.

If a drop of such semen is placed in a glass slide, converted into a hanging drop for placement on a small gas chamber with inlet and outlet, adapted for microdissecting micropipette on the microscope stage, and carbon dioxide is passed into the chamber about the hanging drop, all sperm movement instantly ceases. Replacement with air restores all movement at once. This was shown originally to be a result of an intrinsic, nontoxic effect of carbon dioxide.[1]

With phase contrast microscopy, which facilitates the visualization of the sperm in the living state, this immobilization enables one to readily aspirate a single sperm from its normal environment for study. As an aid in overcoming infertility in men with marked oligospermia, Lawe-King et al.[2] achieved for the first time unequivocal in vitro fertilization of the mature human oocyte by microinjection of a single sperm via the zona pellucida into the perivitelline space. The immobilization technique cited above might well facilitate the aspiration of the single, capacitated sperm for in vitro fertilization.

To aid the man who is the last male member of a family tree, from the lot of immobilized sperm, a Y chromosome containing gamete could be aspirated for in vitro fertilization. The X and Y sperm are clearly discernable in phase contrast by the size and shape of their respective heads: the Y sperm head in profile is likened to a truncated gothic arch; the X sperm is more wedge-shaped in outline. In face view both are oval, the X is larger. The Y sperm has a longer tail as shown with a map measurer in enlarged photographs of each type. The quinacrine hydrochloride stain showed the smaller-headed sperm to contain the fluorescent spot, indicative of the Y chromosome. The smaller headed, lighter Y sperm with longer tail swims faster than the larger, heavier, shorter tailed X sperm.[3]

Landrum B. Shettles, MD, PhD

Womens Hospital, 2025 East Sahara Ave., Las Vegas, NV 89104

REFERENCES

1. Shettles LB. Carbon dioxide tension and its relation to quiescence of spermatozoa in vivo. Proc Soc Exper Biol Med, 1940;45:318-22.
2. Laws-King A, Trounson A, Sathananthan H, Kola I. Fertilization of human oocytes by microinjection of a single spermatozoon under the zona pellucida. Fertil Steril 1977;48:637-42.
3. Shettles LB. Sperm morphology, cervical milieu, time of insemination and sex ratios. Andrologie 1973;5:227-30.

Prolongation of pregnancy and survival of second twin

To the Editors: It would appear that some overseas authors are as uninformed of our literature as we are sometimes of theirs. Despite the claim of Feichtinger et al. (Feichtinger W, Breitenecker G, Fröhlich H. Prolongation of pregnancy and survival of twin B after loss of twin A at 21 weeks' gestation. Am J Obstet Gynecol 1989;161:891-3) that placement of a cerclage after the delivery of an immature first twin was a previously unreported unique aggressive approach, this technique has been included in at least 10 case reports in the American literature.[1-3] The longest interval between deliveries of multiple gestations in the American literature has been 99 days,[2] in contrast to the authors' 12 weeks. Unfortunately, maternal deaths caused by sepsis can occur after cerclage.[4] Judging from comments at the Ninth Annual Meeting of the Society of Perinatal Obstetricians, February 2-4, 1989, New Orleans, Louisiana, the authors' procedure has recently been done many times. It is not without its risks.

Robert C. Goodlin, MD

City and County of Denver, Department of Health and Hospitals, 777 Bannock St., Denver, CO 80204-4507

REFERENCES

1. Banchi MT. Triplet pregnancy with second trimester abortion and delivery of twins at 35 weeks gestation. Obstet Gynecol 1984;64:728-30.
2. Simpson CW, Olatunbosun OA, Baldwin WJ. Delayed interval and delivery in triplet pregnancy: report of a single case and review of the literature. Obstet Gynecol 1984; 64(suppl):8s-11s.
3. Cardwell MS, Caple P, Baker CL. Triplet pregnancy with delivery on three separate days. Obstet Gynecol 1988;71: 448-9.
4. Dunn LJ, Robinson C, Steer CM. Maternal death following suture of incompetent cervix during pregnancy. Am J Obstet Gynecol 1959;78:335-9.

Reply

To the Editors: We thank Dr. Goodlin for his interest in our single case report.

The three references quoted all refer to triplet pregnancies, which may indeed be different from twin pregnancies. The third reference refers to a triplet pregnancy where the infants were delivered on three consecutive days, and it is not at all similar to our case. Obviously, cerclage, particulary in the presence of ruptured membranes, carries significant risks to the mother. However, in the 30 years since reference 4 was published, there have been advances in antibiotic treatment and fetal surveillance.

We would be very interested in corresponding with other obstetricians who have done procedures similar to ours.

Wilfried Feichtinger, MD
Trauttmansdorffgasse 3A, A-1130 Vienna, Austria

Correction

In the article by Tulandi et al., "Treatment-dependent and treatment-independent pregnancy among women with periadnexal adhesions" (AM J OBSTET GYNECOL 1990;162:354-7), on page 355 in the right-hand column of text, line 15 "in the nontreated group (n = 67)..." should have been "(n = 49)..." and line 16 "in the treated group (n = 34)..." should have been "(n = 37)...." On page 356, in Table II under the Intrauterine column of Treated pregnancy, the number 12 should have been 19, the number 3 should have been 4, 60.0% should have been 95.0%, and 15.8% should have been 21.0%. Under the Ectopic column, the number 1 and 5.3% in the bottom row of the table should have been deleted and replaced with —.

ITEMS

Announcements of major meetings and other significant activities must be received at least 8 weeks before the desired month of publication. All announcements carry a charge of $60.00 U.S. per insertion and the fee must accompany the request to publish. Information will be limited to title of meeting, date, place, and an address to obtain further information. Send announcements and payment, payable to this JOURNAL, to Kay G. Goehler, Senior Manuscript Editor, Journal Editing, Mosby–Year Book, Inc., 11830 Westline Industrial Drive, St. Louis, Missouri 63146-3318.

II Course on Molecular Biology of Hormone Action in Endocrinology and Pharmacology, Milan, Italy, October 10-12, 1990. For further information please contact: Organizing Secretariat, Fondazione Giovanni Lorenzini, Via Monte Napoleone, 23, 20121 Milan, Italy. Tel.: 02/76.00.22.67 and 78.38.68. Fax: 02/78.15.11.

Reproductive Scientist Training Program. The Reproductive Scientist Training Program is sponsored by the American College of Obstetricians and Gynecologists, the American Fertility Society, the American Gynecological and Obstetrical Society, the Association of Professors of Gynecology and Obstetrics, the Council on Resident Education in Obstetrics and Gynecology, GynoPharma Incorporated, the APGO Medical Education Foundation, the Society for Gynecologic Investigation, and the National Institute of Child Health and Human Development. This training program is designed to facilitate research training of obstetrician-gynecologists in contemporary research approaches and techniques, and to further progress in the reproductive sciences in medical school departments of obstetrics and gynecology. The areas of research interests covered by the program are broadly defined, but the emphasis in this training will be in cell and molecular biology as applied to problems in reproductive endocrinology, genetics, maternal-fetal medicine, oncology, infectious disease, or other aspects of reproduction. Specifically we wish to attract promising physicians in their fourth year of obstetric-gynecologic residency or near completion of a subspecialty fellowship who desire, in addition to their clinical skills, to develop strong basic science research skills and understanding in fields such as cell and molecular endocrinology, genetics, immunology, and oncology as related to reproductive medicine. This program will consist of 2 years of basic research training after completion of a residency in obstetrics and gynecology or subspecialty fellowship. These initial 2 years of laboratory investigation will be followed by a 3-year period in a department of obstetrics and gynecology, during which time the individual will be expected to spend at least 75% time in research, with the balance for clinical activity. Thus the complete program entails a 5-year commitment to basic science research. We wish to attract promising physicians who will have completed an approved 4-year residency program and who desire to spend several years developing strong basic science research skills in addition to their clinical skills, and who are committed to a career in academic obstetrics and gynecology. Women and minorities are encouraged to apply. For more information please write: Executive Director, Association of Professors of Gynecology and Obstetrics, 409 12th St., SW, Washington, DC 20024. Deadline for applications is October 15, 1990; to start July 1, 1991.

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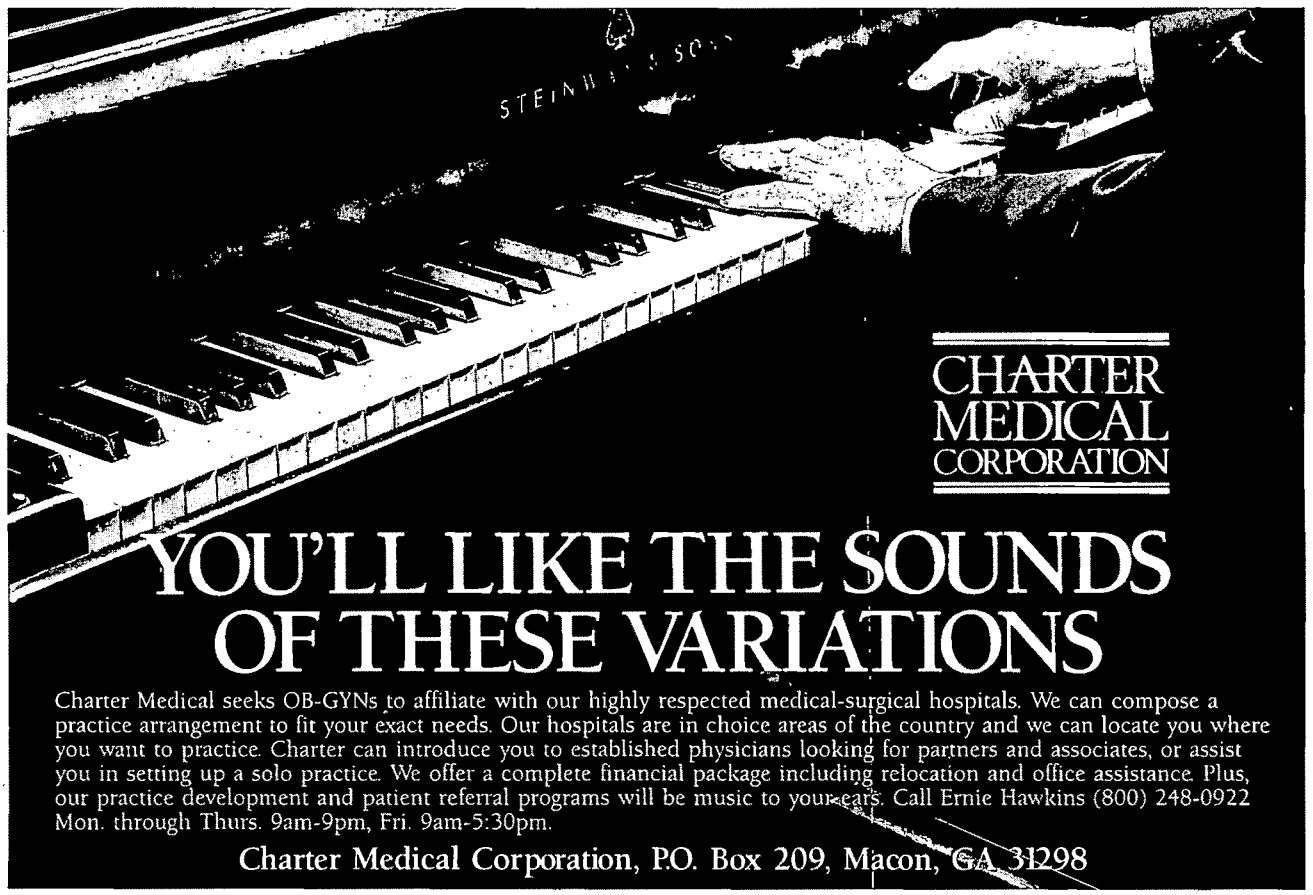
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BC/BE American trained OB/GYN sought to join a busy two-man practice in the scenic Blue Ridge Mountains by a modern 150 bed hospital with over 500 deliveries a year and very active GYN surgical service, including Laser. Excellent opportunity for the right person interested in this area bordering western North Carolina.

Send inquiries and C. V. to:

GALAX OBSTETRICS AND GYNECOLOGY, INC.
106 Doctors Park
Galax, VA 24333

Join us.

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND, a 375,000-member prepaid group practice, currently has a position available for an Obstetrician/Gynecologist. We are a multi-specialty organization located in the scenic Seattle area.

To inquire, write to:
Manager, Medical Staff Personnel
Group Health Cooperative
of Puget Sound
521 Wall Street
Seattle, WA 98121

Group Health Cooperative of Puget Sound

Affirmative Action/Equal Opportunity Employer

PRIVATE PRACTICE OPPORTUNITIES CHICAGO SUBURB

A large, successful multi-specialty group is seeking to add three BC/BE OB/GYNs between now and the summer of 1991. The group currently has three OB/GYNs, but requires additional physicians due to expansion.

This aggressive group is located in Hoffman Estates, a high-growth western suburb of Chicago. Hoffman Estates and the adjoining community of Schaumburg lie at the heart of a "golden corridor" of northwest suburban expansion, a pathway of commercial and residential progress. You'll also enjoy the advantages of living so close to Chicago, one of the country's most exciting cities, offering outstanding cultural, educational and recreational amenities.

For more information about these rewarding private practice opportunities, send your CV to: Paul Coogan, Professional Relations, Humana Inc., Dept. QQ-7A, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

Humana®

KERN MEDICAL CENTER

PROGRAM DIRECTOR
OB/GYN RESIDENCY PROGRAM

Kern Medical Center, a 240-bed county teaching hospital is seeking a Program Director for 8-member OB/GYN Residency Program. Emphasis on general OB/GYN; 5,000 deliveries per year. Mid-sized urban community in Central California; moderate cost of living. Requires administrative or teaching experience. Academic rank and salary commensurate with experience. Supplemental faculty practice plan. Send inquiries and C.V. to:

Ram Ayyagari, M.D., Chairman
Department of Obstetrics & Gynecology
KERN MEDICAL CENTER
1830 Flower St.
Bakersfield, CA 93305
(805) 326-2236

SUPERIOR PRACTICE OPPORTUNITY FOR A GYNECOLOGIST IN BEAUTIFUL, HISTORIC, CHARLESTON, SOUTH CAROLINA

A unique practice opportunity is available for a board certified GYNECOLOGIST to share office space with a well established, progressive (board certified) GYNECOLOGIC ONCOLOGIST.

- Well located, attractive office with common waiting room and business space with six (6) examining rooms and two physician's offices.
- Pleasant professional atmosphere.
- Shared on-call coverage available.
- Close proximity to two (2) JCAH accredited hospitals and Medical University.
- Located in Charleston, S.C., enjoy the cultural and recreational amenities of a cosmopolitan lifestyle, complimented by affordable housing, outstanding educational facilities, and a year round temperate climate.
- Near Kiawah, Seabrook, and Hilton Head Island Resorts.
- S.C. Malpractice rates lower than other areas.

To learn more about this unique practice opportunity, please call or forward your curriculum vitae to:

Myron Lutz, M.D.
1606 Ashley River Road
Charleston, S.C. 29407
803/556-4380

OB/GYN
Northeastern Wisconsin

18 physician multi-specialty group located in a medium-sized Lake Michigan community seeks a second and third BC/BE physician to join its department of Obstetrics and Gynecology. Positions offer an excellent professional, financial and life-style opportunity. Send C.V. or call James Robinson, Administrator, Manitowoc Clinic, 601 Reed Avenue, Manitowoc, WI 54220. Telephone: (414) 682-8841.

Ambulatory Gynecologist

Marshfield Clinic's Department of OB/GYN is expanding and is seeking a board-certified obstetrician/gynecologist for a new Ambulatory Gynecology position. Primary responsibilities include walk-in ambulatory patients, performance of diagnostic office procedures, directing the departments' physician extender clinic, and initial infertility evaluations. No OB or GYN call; no obstetrical care. Marshfield Clinic is a 350 physician multi-specialty private group located in a thriving family-oriented community in central Wisconsin. Please send curriculum vitae to:

George L. Hill, M.D.
Chairman OB/GYN Department
1000 North Oak Avenue
Marshfield, WI 54449
or call collect
(715) 387-5161

Marshfield Clinic

Postdoctoral Training Program in Medical Genetics

The Interdepartmental Medical Genetics Program at Stanford University School of Medicine provides advanced clinical and/or research training related to human inherited disease. Well-represented areas of the program include:

- The molecular basis of heritable disorders including polygenic and multifactorial diseases.
- Chromosome structure and function.
- Genome and gene mapping.
- The development of methods to manipulate and to study large fragments of DNA.
- Developing animal models and new treatment modalities of human genetic disease by homologous recombination.

Individuals with an MD, PhD, or equivalent degree are eligible for this three-year program which includes an extended period of research training with one of twenty-six training faculty and the opportunity to pursue applied training in clinical genetics, clinical cytogenetics, or molecular genetics in an ABMG-accredited setting. Minority individuals are especially encouraged to apply. For information and application forms, contact:

Uta Francke, M.D.
Departments of Genetics and Pediatrics
Howard Hughes Medical Institute
Stanford, California 94305-5428

Fargo Clinic
MeritCare

OB-GYN

Large multispecialty group is seeking BC/BE Obstetrician-Gynecologist to join seven member department. Department is active in donor and husband insemination. Opportunity to develop Invitro and Gift Programs available.

Fargo Clinic is a 250 physician group that practices in 30 locations throughout eastern ND and western MN. The main facility is located next to St. Luke's Hospitals, a 400 bed tertiary care & trauma center. St. Luke's is a NACHRI designated Children's Hospital with a level III ICN.

Fargo-Moorhead is a tri-college community of 130,000 located just minutes from the lake country of western Minnesota. Abundant cultural, recreational, sporting and hunting activities available year around.

Outstanding compensatory package available. Respond to Robert C. Montgomery, M.D., Chairman, Physician Recruitment, 737 Broadway, Fargo, ND 58123.

SPECIAL DELIVERIES. SPECIAL CHALLENGES.

The Southern California Permanente Medical Group invites you to join a unique prepaid health care program. Our multispecialty group practice is a partnership composed of and managed by SCPMG physicians.

Board eligible/certified **PERINATOLOGISTS** are needed for our high-volume obstetric services which handles 3,000-6,000 deliveries per year. Opportunities exist both to join and create high risk services.

There are positions available to practice Perinatology exclusively. Perinatologists who are interested in performing other aspects of obstetrics and gynecology may do so. We also have positions available for Endocrinologists and General Obstetrician-Gynecologists. University affiliation and clinical research are encouraged.

Our compensation is competitive and benefits are outstanding. They include: professional liability, medical and dental coverage, vacation and sick leave, continuing education, life insurance and retirement plans. **After two years full-time employment, physicians are eligible to be considered for partnership.**

For a physician application, please call (800) 328-5278. If calling from outside of California, please (800) 541-7946 or send curriculum vitae to: Irwin P. Goldstein, M.D., Associate Medical Director, SCPMG, Dept. 006, Walnut Center, Pasadena, CA 91188-8013. Equal Opportunity Employer M/F/H

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Good People. Good Medicine.

OB/GYN HITCHCOCK CLINIC

Outstanding opportunity for BC/BE Ob-Gyn physician to join a busy general Ob-Gyn practice in rural Vermont. Association with board certified Ob-Gyn. Employment through Hitchcock Clinic offers guaranteed income, benefits and faculty appointment at Dartmouth Medical School. Randolph, Vermont is centrally located to most of Vermont's major ski areas, but off the tourist track. Convenient to Boston and Montreal. Many practice and lifestyle advantages other practice opportunities cannot provide.

For information contact: Brent Burgee, M.D., Hitchcock Associates of Randolph/ Ob-Gyn, 1 Maple Street, Randolph, Vermont 05060; (802) 728-4431.

An equal opportunity/
affirmative action employer

Dartmouth-Hitchcock Medical Center
The Hitchcock Clinic, Hanover

OB/GYN
WISCONSIN

Multi-specialty group in suburban Milwaukee seeks BC/BE Obstetrician/Gynecologist to join 6 physician OB/GYN department. Single site, single hospital practice. Competitive salary and fringe benefits. Forward inquiries and CV to:

Administrator
P.O. Box 427
Menomonee Falls, WI
53051

NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting for positions in our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

REPRODUCTIVE ENDOCRINOLOGIST

• SAN JOSE •

We are currently seeking a Reproductive Endocrinologist to establish and run a reproductive endocrinology subdivision in the department. Duties would include the full spectrum of reproductive endocrinology, outpatient and surgical management of infertility. Fellowship certification would be preferred. The department currently has 17 physicians and is still growing. We offer a generous benefits package including full coverage malpractice insurance. San Jose has beautiful weather and excellent access to Bay Area recreational and cultural activities.

For more information, please contact: Jerome L. Nehemiah, M.D., Chief, Department of OB/GYN, The Permanente Medical Group, Inc., 260 International Circle, Dept. AJOBG, San Jose, CA 95119, or call collect (408) 972-6180. EOE

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OB/GYN

Free yourself from the business aspects of private practice and enjoy the visibility and advantages of a multi-specialty prepaid group practice in SUBURBAN BOSTON. Experience reasonable work and coverage schedules. As a full-time member of our respected staff, you will work in one of our modern, well-equipped facilities in north suburban or south suburban Boston. Ancillary services are on-site. Locations are within reasonable distance of the ocean, ski resorts, cultural and academic centers. Excellent compensation and fringe benefit package including full malpractice coverage. **Send C.V. to Director of Physician Recruitment, Medical East Community Health Plan, One Worcester Road, Framingham, MA 01701; or call collect (508) 879-0077.**

Medical East™
Community Health Plan
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Finger Lakes Region
Ithaca, New York

Unique opportunity for patient oriented physician in comprehensive OB-GYN service, building on established patient base of 6,000 patients. To include out-patient gynecology, obstetrics, surgery, infertility, and abortions. First call protection from nurse-midwives. Progressive university community (home of Cornell University) offers cultural attractions of a city with the benefits of small town living. Competitive salary, excellent benefits including malpractice. Summer/Fall 1991.

Send CV To: Joyce Leslie, M.D., Planned Parenthood of Tompkins County, 314 W. State St., Ithaca, NY 14850.

Planned Parenthood®
of Tompkins County

PERINATOLOGIST

Denver, Colorado

Rose Medical Center, Denver, Colorado is seeking a second BE/BC perinatologist to work full-time in a 400-bed private community hospital adjacent to the University of Colorado Health Sciences Center. With 3,600 deliveries per year, and 27 University Residents rotating through the department annually, Rose is the major private teaching affiliate of the University.

Responsibilities include, primary patient care, private consultation, physician, resident, and nursing education, clinical research, and a limited private practice in perinatology. This individual can expect frequent interaction with the Maternal/Fetal Division at the University of Colorado, and will be eligible for an appropriate clinical appointment at the University. All clinical responsibilities will be shared with the current full-time perinatologist at Rose. Additional call coverage is provided by other perinatologists in the Denver metro area.

A competitive salary guarantee is being offered, with excellent fringe benefits including malpractice insurance.

Qualified applicants, individuals completing fellowship in June, 1991, should forward CV's to:

Robert E. Wall, M.D., Chairman
Department of Obstetrics & Gynecology
Rose Medical Center
4567 East Ninth Avenue
Denver, Colorado 80220
Telephone: (303) 320-2077

—A WELL-KEPT SECRET —
The Blue Water Coast

Port Huron Hospital and its medical staff are seeking two board certified/eligible Obstetrician/Gynecologists to join their thriving community. Port Huron Hospital is a full service, 264-bed regional health care facility with 27 post-partum beds, birth centers, a Level II special care nursery and averages 1,600 births annually.

The geography will be appealing to those who are fascinated by large bodies of water. The City of Port Huron, Michigan, is ideally situated on the Canadian border at the southern end of beautiful Lake Huron, just fifty minutes from metropolitan Detroit. The international Blue Water Bridge provides immediate access to the Province of Ontario.

A highly competitive compensation package is being offered including relocation expenses. Interested candidates should reply to:

Michael R. Donaldson
Director, Physician Recruitment
St. John Outpatient Corporation
31510 Gratiot, Suite 300
Roseville, MI 48066
(313) 296-8610

REPRODUCTIVE ENDOCRINOLOGIST

St. Luke's/Roosevelt Hospital Center is one of New York City's largest voluntary hospitals and affiliated with the Columbia University College of Physicians and Surgeons. The Department of Obstetrics and Gynecology seeks a board certified or board eligible sub-specialist to direct the Division of Reproductive Endocrinology. The Department has approved residency and medical student training programs. The Hospital offers an attractive location on West Side of Manhattan. Salary, hospital and university appointments will be commensurate with qualifications and experience. Contact

Robert S. Neuwirth, M.D.
Director, Obstetrics and Gynecology
c/o Josephine Simpson
Human Resources
ST. LUKE'S/ROOSEVELT
HOSPITAL CENTER
114th Street and Amsterdam Avenue
New York, NY 10025

An Equal Opportunity Employer M/F.

MATERNAL-FETAL MEDICINE

The Department of Obstetrics and Gynecology at the University of Tennessee Medical Center at Knoxville is currently recruiting one or two additional BC/BE specialists in Maternal-Fetal Medicine.

This is the chance to join a young, growing, dynamic program which encourages active participation in resident and outreach education and offers ample opportunity for basic and clinical research. More than 700 procedures are done monthly in the Department's autonomous Obstetrical Ultrasound and Antenatal Assessment Unit. Constuction of a new Labor and Delivery suite is expected to be completed in January of 1991.

A highly competitive compensation package, coupled with relatively low malpractice insurance, and proximity to many recreational facilities in beautiful East Tennessee makes this an extremely attractive opportunity for the person interested in combining a rewarding academic career and a full family life.

Academic rank is commensurate with qualifications and experience. Interested persons should send C.V. or inquiries to:

Kenneth F. Trofatter, Jr., MD, PhD
Associate Professor and Director
Maternal-Fetal Medicine
Department of Obstetrics & Gynecology

THE UNIVERSITY OF TENNESSEE
Medical Center at Knoxville

1924 ALCOA HIGHWAY
KNOXVILLE, TENNESSEE 37920
For more information call (615) 544-9300.
EEO/An Affirmative Action/Title IX/Section 504 Employer

OB-GYN

BC/BE OB-GYN sought for full service, 260-bed community hospital in San Francisco's dynamic South of Market area.

- Excellent opportunity to join busy, growing practice.
- Competitive salary and benefits package.

ST. LUKE'S HOSPITAL

Send C.V. to:

Walter Kopp
St. Luke's Hospital
3555 Army Street
San Francisco, CA 94110
(415) 641-6543

Gynecologic Oncologist
Philadelphia, Pennsylvania

Progressive, rapidly expanding Division of Gynecologic Oncology located in Center City has full-time academic position available. Candidates must be Board Eligible/Certified gynecologic oncologists. Recruitment at Assistant/Associate Professor level. Excellent clinical and research opportunities available. Competitive salary and benefits program.

Interested persons send curriculum vitae to:

John A. Carlson, Jr., M.D.
Director, Division of
Gynecologic Oncology
Thomas Jefferson University
School of Medicine
Department of Obstetrics
and Gynecology
1025 Walnut Street
Medical College Building-Room 310
Philadelphia, PA 19107

Director Perinatology—Virginia Beach General Hospital. Develop new birthing center/department with already established NICU. Staffed by two neonatologists and 20 active OB/GYNs. This 263-bed full-service community hospital sees 3.5K deliveries per year and is part of a two-hospital network with excess of $150 million annual revenues. On the coast, this comfortable, stimulating community of 1.5 million is supported economically by the nation's largest naval industrial complex and is within easy access to the Washington, D.C. areas and the Carolinas. The position offers an excellent opportunity to develop a first-rate birthing center in Virginia Beach with office space adjoining the hospital. Excellent compensation package plus relocation. Experienced directors/leaders preferred. Contact Steve George, Tyler & Company, 9040 Roswell Road, Suite 550, Atlanta, GA 30350. (404) 641-6416.

Obstetrics/ Gynecology

WISCONSIN: Marshfield Clinic, a multi-specialty group practice with 350 physicians is seeking BE/BC obstetricians/gynecologists to join expanding (40-50 physician) regional centers in Chippewa Falls and Woodruff, Wisconsin. A third OB/GYN is needed for each facility. Chippewa Falls is located 1 1/2 hours from downtown Minneapolis/St. Paul and twenty minutes from a major four year campus of the University of Wisconsin. Known as the "Lakeland Area" (over 1,000 navigable lakes) Woodruff is truly one of the most attractive vacation areas in the upper Midwest and renown for its year-round outdoor recreational activities. Both communities offer exceptional recreational, cultural, and educational opportunities. An emphasis on quality practice and life-style is combined with a total compensation package on reaching membership in excess of $200,000. Starting salary negotiable. Fringe benefit package outstanding; includes self-insured malpractice. No start-up expense. Send C.V. and references to:

David L. Draves
Director, Regional Development

1000 North Oak Avenue
Marshfield, Wisconsin 54449
or call collect at
(715)387-5376

Marshfield Clinic

CASE WESTERN RESERVE UNIVERSITY AND UNIVERSITY MACDONALD WOMENS HOSPITAL

1. Director, Division of Maternal-Fetal Medicine
2. Perinatologist with ultrasound/doppler experience
3. Gynecologic Oncologist
4. Ob/Gyn Generalist (2 Positions)

An outstanding and exciting opportunity exists for ob/gyns seeking full-time academic careers in one of the leading medical centers in the United States. The Department of Obstetrics and Gynecology at University Hospitals of Cleveland and Department of Reproductive Biology of Case Western Reserve University is under new leadership and is recruiting faculty to work in a University-affiliated, Level III hospital which is just completing the final phase of an extensive remodeling program. The positions include faculty appointments at the rank of Assistant, Associate or Full Professor, depending upon academic credentials. An excellent salary, incentive and benefit package is being offered. Board certified or eligible candidates should send their curriculum vitae to:

Wulf H. Utian, M.D., Ph.D.
Department of Ob/Gyn
University Hospitals of Cleveland
2074 Abington Road
Cleveland, OH 44106

The University and Hospital are equal opportunity, affirmative action employers, women and minorities are encouraged to apply.

FACULTY POSITIONS FOR BOARD CERTIFIED OR ELIGIBLE

DIRECTOR, MATERNAL-FETAL DIVISION
PERINATOLOGIST
REPRODUCTIVE ENDOCRINOLOGIST
OB/GYN GENERALIST

These physicians will devote time to clinical practice, resident and medical student teaching programs and research.

Academic level will be in accordance with experience and achievement.

Excellent salary combines base-line and practice incentive plan plus a comprehensive benefit package.

Applicants should send curriculum vitae to:

John W. Greene, Jr., M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
University of Kentucky Medical Center
800 Rose Street, MN318
Lexington, KY 40536-0084

THE UNIVERSITY OF KENTUCKY IS AN AFFIRMATIVE ACTION, EQUAL OPPORTUNITY EMPLOYER AND ACTIVELY SEEKS THE CANDIDACY OF MINORITIES AND WOMEN.

FACULTY POSITIONS IMMEDIATELY AVAILABLE

Maternal Fetal Medicine — Reproductive Endocrinology — Obstetrics/Gynecology — Urogynecology

The Department of Obstetrics and Gynecology at the University of South Dakota School of Medicine in Sioux Falls, South Dakota, a delightful city located directly on the Sioux River and serving a tri-state area and one of the best kept secrets in the Midwest, is building a full-time academic department. Qualified individuals to contribute, develop and provide leadership in all aspects of the specialty are actively being sought.

Candidates should have interests in clinical practice activities and medical education. Clinical and/or basic research opportunities are available and encouraged. An opportunity for a creative, motivated individual with a pioneer spirit.

Financial remuneration and incentives are competitive and commensurate with experience, credentials and rank. BC or BE. Position open until filled.

Please send Curriculum Vitae to: R. H. Wiebe, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, University of South Dakota School of Medicine, 1100 South Euclid Avenue, Sioux Falls, SD 57117-5039, (605) 333-7327.

An Equal Opportunity/Affirmative Action Employer

OBSTETRICIAN/ GYNECOLOGIST

Board certified or board eligible obstetrician/gynecologist to join two member department in multispecialty clinic. Office ultrasound, colposcopy, and cryosurgery available. Adjacent to 94 bed community hospital with special care nursery.

Worthington, MN is a community of 11,000 located in the highly productive corn belt. Recreational activities include good hunting, fishing, and two 18 hole golf courses. Excellent schools, pollution free environment, with low crime rate make this an ideal community for family living.

Excellent compensation package available. Respond to Mr. John Sieve, Administrator, Worthington Medical Center, 508 10th Street, Worthington, MN 56187 or call 507-372-2921.

FACULTY OPENINGS
IN
OBSTETRICS & GYNECOLOGY
FOR
GENERALISTS/PERINATOLOGISTS

Full time faculty positions at the University of South Alabama, Department of Obstetrics & Gynecology. Excellent opportunity for teaching, research and clinical service. Individuals must be board eligible or certified in Specialty/Sub-specialty. The academic rank and salary will be dependent upon the training and experience of the applicant. These positions are available immediately.

Please contact:

Ian H. Thorneycroft, Ph.D., M.D.
Professor and Chairman
Department of Ob-Gyn
University of South Alabama
College of Medicine
2451 Fillingim Street
Mobile, Alabama 36617
(205) 471-7943

University of South Alabama
is an Equal Opportunity Employer

OB/GYN BC/BE two positions available in Oklahoma for hospital based practice. New, fully equipped, LDRP facility, with central fetal monitoring, telemetry, dedicated staff and 24 hour obstetrical anesthesia and family prenatal classes. Level I and II nurseries, strong Pediatrician support. Progressive community with college, symphony and cultural opportunities. Malpractice rates reasonable. Salary and benefits guaranteed. Reply with CV to Medical Staff Office, Room 3122, P.O. Box 205, Oklahoma City, Oklahoma 73101.

OBSTETRICIAN/GYNECOLOGIST
OPPORTUNITY AVAILABLE
SAGINAW, MICHIGAN

St. Luke's Hospital is actively recruiting board certified/board eligible OB/GYNs for the newly established maternity department. An excellent salary, malpractice insurance, health insurance and moving expenses are among the many benefits that this opportunity offers.

St. Luke's Healthcare Association, a 414-bed multifacility system, anticipates opening the new 10-bed LDRP unit in early 1991. Saginaw is located 100 miles northwest of Detroit and 15 miles south of the Saginaw Bay near Michigan's "Thumb."

For more information, in confidence, respond with curriculum vitae or call: Debra Hartman, Bronson Management Services Corporation, 210 East Vine Street, Kalamazoo, Michigan 49001 (800) 594-9022.

StLukes
Hospital

OBSTETRICIAN/ GYNECOLOGIST

Immediate opening for a Board Certified/Eligible physician to work with 5 others at a well-established, growing HMO. Rochester Medical Group is a multispecialty medical group practice serving 45,000 patients at multiple sites. Clinical faculty appointment at the University of Rochester is available with this position. Competitive salary/ benefits with opportunities for research and resident teaching. Send resume to:

Patricia Hosking
Rochester Medical Group, PC
1800 Hudson Avenue
Rochester, NY 14617

KALAMAZOO, MICHIGAN

Seeking Medical Director for Planned Parenthood outpatient surgical clinic. Services include reproductive health care, abortions and sterilizations. Limited call. Paid malpractice insurance, competitive salary and complete benefit package.

Kalamazoo, a university community located midway between Chicago and Detroit, has a county population of 220,000. Lake Michigan's sandy beaches are only minutes away and numerous lakes, hills and forests provide boundless recreational activities. Excellent schools.

For more information send CV or call:
Judy Van Noordwyk, R.N.
Bronson Management
210 East Vine Street
Kalamazoo, Michigan 49001
800-594-9022 or
616-344-6444 collect



Regional Director, Women's Services

(OB/GYN)

Kaiser Permanente offers the advantage of joining the largest and most successful pre-paid group medical practice in America. We also provide the opportunity to play an integral role in shaping the Obstetrical & Gynecological Services offered in our northeastern Ohio region—210,000 patient members and growing. This Regional Department Chairman will establish and implement an ongoing program of Women's Services. Our selected candidate will provide outstanding clinical leadership to a department of 23 physicians; identify long and short-term human resource needs; actively direct staff recruiting for Obstetrics and Gynecology; ensure the implementation of Quality Improvement efforts; and fully manage patient service delivery within the region. We offer attractive salary and superb benefits plus relocation to northeastern Ohio, where a thriving metropolitan setting and an excellent housing climate provide a high quality of life. For consideration please submit your resume, in confidence, to: **Ronald G. Potts, M.D., Medical Director, Ohio Permanente Medical Group Inc., Dept. HROBGYN, 1300 E. 9th St., Suite 1100, Cleveland, Ohio 44114. Or call us at 1-800-837-OPMG/(216) 623-8770.** EOE.

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The Ohio Permanente Medical Group, Inc.

KAISER PERMANENTE

OBSTETRICIAN-GYNECOLOGIST

The Permanente Medical Group, Inc., of San Jose, California is looking for BC/BE physicians for immediate openings in the OB/GYN Department. Positions available either at the main facility in San Jose, or at satellite medical offices in Gilroy. The young, dynamic, department is still growing and currently has seventeen physicians and two nurse practitioners. Our outstanding benefits package includes full coverage malpractice insurance. San Jose and Gilroy share excellent access to Bay Area cultural and recreational activities.

Recent salary advances allow extremely competitive compensation starting with the first year of employment.

For more information, please contact:

Jerome L. Nehemiah, M.D.
Chief, Department of Ob/Gyn
The Permanente Medical Group, Inc.
260 International Circle
San Jose, CA 95119
or telephone: 408-972-6180 (collect)

OBSTETRICIAN GYNECOLOGIST

Western Massachusetts staff model Health Maintenance Organization is seeking two full-time, Board Certified/Board Eligible Obstetrician/Gynecologists to join our expert staff of five physicians and five midwives.

Our multi-specialty group practice employs 70 full-time physicians and provides care for a membership of over 65,000 patients in our modern suburban facilities. Inpatient care is provided at a 900-bed Tufts affiliated teaching hospital.

Attractive Pioneer Valley location with fine educational, cultural and recreational opportunities. Excellent salary and comprehensive benefit program. Please send curriculum vitae to: Oded Rencus, M.D., Chief of OB/GYN, 305 Bicentennial Highway, Springfield, MA 01118 or call (413) 594-3111.

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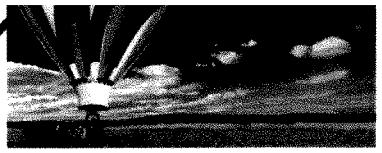
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:ONTRAINDICATIONS: Oral contraceptives should not be used in women who currently have the following onditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophle- ıitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected arcinoma of the breast. 5. Carcinoma of the endometrium or other known or suspected estrogen-depen- ent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Cholestatic jaundice of pregnancy or jaundice vith prior pill use. 8. Hepatic adenomas or carcinomas. 9. Known or suspected pregnancy.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

he use of oral contraceptives is associated with increased risks of several serious conditions including nyocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the sk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The sk of morbidity and mortality increases significantly in the presence of other underlying risk factors such s hypertension, hyperlipidemias, obesity and diabetes. Practitioners prescribing oral contraceptives hould be familiar with the following information relating to these risks. The information contained in this rief summary is principally based on studies carried out in patients who used oral contraceptives with ıgher formulations of estrogens and progestogens than those in common use today. The effect of long erm use of the oral contraceptives with lower formulations of both estrogens and progestogens remains o be determined. Throughout this brief summary epidemiological studies reported are of two types: etrospective or case control studies and prospective or cohort studies. Case control studies provide a ıeasure of the relative risk of a disease, namely a *ratio* of the incidence of a disease among oral contra- eptive users to that among nonusers. The relative risk does not provide information on the actual clinical ıccurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in he incidence of disease between oral contraceptive users and nonusers. The attributable risk does pro- ide information about the actual occurrence of a disease in the population. For further information, the eader is referred to a text on epidemiological methods. 1. THROMBOEMBOLIC DISORDERS AND OTHER 'ASCULAR PROBLEMS. a. Myocardial Infarction. An increased risk of myocardial infarction has been ssociated with oral contraceptive use. This risk is primarily in smokers or women with other underlying sk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and iabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two o six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has een shown to contribute substantially to the incidence of myocardial infarctions in women in their nid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated vith circulatory disease have been shown to increase substantially in smokers, especially in those 35 ears of age and older among women who use oral contraceptives. Oral contraceptives may compound the ffects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In articular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, vhile estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase lood pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been ssociated with an increased risk of heart disease. Oral contraceptives must be used with caution in vomen with cardiovascular disease risk factors. b. Thromboembolism. An increased risk of thromboem- olic and thrombotic disease associated with the use of oral contraceptives is well established. Case ontrol studies have found the relative risk of users compared to non-users to be 3 for the first episode of uperficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for vomen with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the elative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospital- :ation. The risk of thromboembolic disease associated with oral contraceptives is not related to length of se and disappears after pill use is stopped. A two- to four-fold increase in relative risk of post-operative hromboembolic complications has been reported with the use of oral contraceptives. The relative risk of enous thrombosis in women who have predisposing conditions is twice that of women without such ıedical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and or two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and uring and following prolonged immobilization. Since the immediate postpartum period is also associated vith an increased risk of thromboembolism, oral contraceptives should be started no earlier than four veeks after delivery in women who elect not to breast feed. c. Cerebrovascular diseases. Oral contracep- ves have been shown to increase both the relative and attributable risks of cerebrovascular events hrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), ypertensive women who also smoke. Hypertension was found to be a risk factor for both users and on-users, for both types of strokes, and smoking interacted to increase the risk of stroke. In a large study, he relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for sers with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non- mokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for mokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hyper- ension. The attributable risk is also greater in older women. d. Dose-related risk of vascular disease from ral contraceptives. A positive association has been observed between the amount of estrogen and rogestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density poproteins (HDL) has been reported with many progestational agents. A decline in serum high density poproteins has been associated with an increased incidence of ischemic heart disease. Because estro- ens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved etween doses of estrogen and progestogen and the activity of the progestogen used in the contraceptive. 'he activity and amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For ny particular estrogen/progestogen combination, the dosage regimen prescribed should be one which ontains the least amount of estrogen and progestogen that is compatible with a low failure rate and the eeds of the individual patient. New acceptors of oral contraceptive agents should be started on prepara- ions containing 0.035 mg or less of estrogen. e. Persistence of risk of vascular disease. There are two tudies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a tudy in the United States, the risk of developing myocardial infarction after discontinuing oral contracep- ves persists for at least 9 years for women 40-49 years who had used oral contraceptives for five or ıore years, but this increased risk was not demonstrated in other age groups. In another study in Great ritain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation f oral contraceptives, although excess risk was very small. However, both studies were performed with ral contraceptive formulations containing 50 micrograms or higher of estrogens. 2. ESTIMATES OF 'ORTALITY FROM CONTRACEPTIVE USE. One study gathered data from a variety of sources which have stimated the mortality rate associated with different methods of contraception at different ages. These stimates include the combined risk of death associated with contraceptive methods plus the risk attribu- able to pregnancy in the event of method failure. Each method of contraception has its specific benefits nd risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke nd 40 and older who do not smoke, mortality associated with all methods of birth control is low and elow that associated with childbirth. However, smokers 35 and older and non-smokers 40 and older who se oral contraceptives have a significant increase in mortality higher than those using other methods of irth control. These facts must be weighed in conjunction with failure rates for other methods and the risk ssociated with subsequent pregnancy. 3. CARCINOMA OF THE REPRODUCTIVE ORGANS. Numerous pidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical ancer in women using oral contraceptives. While there are conflicting reports most studies suggest that se of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. ome studies have reported an increased relative risk of developing breast cancer, particularly at a ounger age. This increased relative risk appears to be related to duration of use. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. 4. HEPATIC NEOPLA- SIA. Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocel- lular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. 5. OCULAR LESIONS. There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immedi- ately. 6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY. Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out. 7. GALLBLADDER DISEASE. Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens. 8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. Oral contra- ceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users. This effect has been shown to be directly related to estrogen dose. Progestogens increase insulin secre- tion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives. A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users. 9. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with extended duration of use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity. Women with a history of hypertension or hypertension-related diseases, or renal disease, should be encouraged to use another method of contra- ception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users. 10. HEADACHE. The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause. 11. BLEEDING IRREGULARITIES. Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, espe- cially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent. 12. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contracep- tive failures. **PRECAUTIONS:** 1. PHYSICAL EXAMINATION AND FOLLOW UP. A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. 2. LIPID DISORDERS. Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. 3. LIVER FUNCTION. If jaundice develops in any woman receiving such drugs, the medica- tion should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function. 4. FLUID RETENTION. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. 5. EMOTIONAL DISORDERS. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 6. CONTACT LENSES. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. 7. DRUG INTERACTIONS. Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifam- pin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines. 8. INTERACTIONS WITH LABORATORY TESTS. Certain endocrine and liver function tests and blood components may be affected by oral contraceptives: a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. b. Increased thyroid binding globulin (TBG) lead- ing to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radio-immunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. c. Other binding proteins may be elevated in serum. d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids, however, free or biologically active levels remain unchanged. e. Triglycerides may be increased. f. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives. 9. CARCINO- GENESIS. See WARNINGS section. 10. PREGNANCY. Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections. 11. NURSING MOTHERS. Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child. **INFORMATION FOR THE PATIENT: See Patient Package Insert. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section). Thrombophlebitis and venous thrombosis with or without embolism. Arterial thromboembolism. Pulmonary embolism. Myocardial infarction. Cere- bral hemorrhage. Cerebral thrombosis. Hypertension. Gallbladder disease. Hepatic adenomas or benign liver tumors. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea. Vomiting. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Amenorrhea. Temporary infertility after discontinuation of treatment. Edema. Melasma which may persist. Breast changes: tender- ness, enlargement, secretion. Change in weight (increase or decrease). Change in cervical erosion and secretion. Diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome. Cataracts. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. Hemolytic uremic syndrome. Acne. Changes in libido. Colitis. **OVERDOSAGE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

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FIRST EUROPEAN CONFERENCE ON SEX STEROIDS AND METABOLISM

Oral Contraceptives in the Nineties: Metabolic Aspects—Facts and Fiction

Esbjerg, Denmark
May 18-20, 1989

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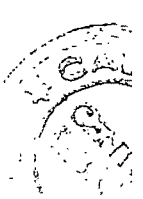
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Oxford, England

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Boston, Massachusetts

The large prospective Nurses' Health Study shows no effect of past oral contraceptive use on risk of cardiovascular disease, which is consistent with a meta-analysis of 13 studies.

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Odense, Denmark

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Leiden, The Netherlands

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Marseille, France

Insulin resistance is a risk factor for atherothrombosis, which could be in part attributed to the increased level of an inhibitor of the fibrinolytic system, plasminogen activator inhibitor.

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Introductory remarks

Jørgen Jespersen, MD, DSc, Sven O. Skouby, MD, DSc, and Cornelis Kluft, PhD

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The first European Conference on Sex Steroids and Metabolism, which was sponsored by the International Sex Steroid Foundation, was organized by the South Jutland University Centre, Esbjerg, and took place at the Ribe County Hospital in Esbjerg, Denmark, on May 18-20, 1989.

These proceedings contain contributions to the conference, which formed the scientific platform for a Consensus Meeting on May 21, 1989. The conclusion of this Consensus Meeting was published in the May 1990 issue of the JOURNAL (162:1335-7).

It was not the purpose of the conference to discuss the effectiveness of the formulations in contraception, which, with all pills, is the primary criterion. It was recognized that in developing new formulations, a driving force has been the clinical and metabolic "side effects" of oral contraceptive agents. These metabolic effects in various systems have not been previously discussed in one meeting and in putative coherence. We attempted this by organizing an interdisciplinary conference of active scientists within the areas of epidemiology, blood coagulation and fibrinolysis, vascular disease, lipid and carbohydrate metabolism, and sex steroids. We believed that by breaking down the traditional separation between these research fields, further progress could be stimulated both with respect to the pathogenesis of cardiovascular diseases and the side effects of oral contraceptives.

This initiative was met with enthusiasm, and more than 200 specialists from all over the world attended the conference. We hope that the present proceedings will be of value not only for the participants, but also for those who were unable to attend the conference.

Finally, we acknowledge the educational grants from the pharmaceutical companies, which made the conference and these proceedings possible. We also express our thanks to those who were actively involved and who successfully performed the tasks delegated to them.

6/0/20792

An epidemiologic survey of cardiovascular disease in women taking oral contraceptives

Margaret Thorogood, BSc, Research Officer, and
Martin P. Vessey, MD, Professor of Social and Community Medicine
Oxford, England

Earlier epidemiologic studies have indicated an increase in mortality from certain cardiovascular diseases in young women associated with the use of oral contraceptives. However, since these studies were conducted, newer oral contraceptives containing less estrogen and progestogen have been widely adopted. In addition, an increasing majority of oral contraceptive use is by women under the age of 30 years. Early results from a new case-control study suggest the possibility that the risk of myocardial infarction associated with oral contraceptive use is now lower than in the past, although the previously observed small increase in the risk of subarachnoid hemorrhage appears to be unchanged. (AM J OBSTET GYNECOL 1990;163:274-81.)

Key words: Oral contraceptives, cardiovascular disease

Since oral contraception first became available nearly 30 years ago, the complicated question of the relationship between oral contraceptive use and cardiovascular disease has been researched extensively. It is beyond the scope of this brief article to review the entire epidemiologic literature on the subject, and therefore we concentrate specifically on the most serious of the possible cardiovascular side effects of oral contraceptives, that is, fatal disease. We review previous studies and then describe how the use of oral contraceptives has changed in Britain and consider how it might affect the risk of cardiovascular disease. Finally, we describe a new case-control study that we are conducting and discuss some of the preliminary results.

Methods

The two most important research strategies that have been used in the study of the relationship between the pill and cardiovascular disease are case-control and cohort strategies. The design of cohort studies is described in Table I. In a cohort study two groups of persons are identified: one group that is exposed to the agent of interest (in this case oral contraceptives) and a control group that is similar to the exposed group in the area of other risk factors for the disease but not exposed to the agent of interest. The two groups are followed up, and the incidence of the disease under study is noted for each group. The relative risk of the disease among those exposed can then be calculated from the ratio of the rate of the disease in the exposed

Table I. Cohort studies

Start with exposure to the suspected agent
Exposed cohort (e.g., those taking pill)
Control cohort (e.g., those not taking pill)—otherwise similar to exposed cohort
Both cohorts followed over time (usually several years)
Incidence of the disease is noted in both cohorts
Relative risk is ratio of incidence rate in exposed cohort to that in the control cohort
Absolute risk is incidence rate in exposed cohort minus incidence rate in control cohort

Table II. Case-control studies

Start by finding cases of the disease
Controls are people without the disease but otherwise similar to the cases
History of exposure to the suspected agent is obtained for both cases and controls
Relative risk is ratio of exposed to nonexposed cases divided by the corresponding ratio in the controls
Absolute risk cannot be calculated

From the Department of Community Medicine and General Practice, University of Oxford.
Supported by the Medical Research Council, the British Heart Foundation, the Committe on Safety of Medicines, and Family Health International.
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Table III. Case-control studies of fatal cardiovascular disease

Reference	*Date*	*Disease*	*N*	*Age range (yr)*	*Data collection*	*Controls*
Inman and Vessey, 1968[1]	1966	VT, TS, MI	334	20-44	By medical officers visiting patients' GPs	Age-matched living women from the same GP
Mann and Inman, 1975[2]; Mann et al., 1976[3]	1973	MI	207	Under 50	As above	As above
Inman, 1979[4]	1976	SAH	134	15-44	As above	As above
Adam et al., 1981[5]; Thorogood et al., 1981[6]	1978	MI, SAH	307	15-44	By correspondence with patients' GPs	As above

GP, General practitioner; *VT*, venous thromboembolism; *TS*, thrombotic stroke; *MI*, myocardial infarction; *SAH*, subarachnoid hemorrhage.

cohort to that in the control cohort. Thus, for example, if 10,000 women were in each group and six subjects in the exposed group developed the disease compared with three in the nonexposed group, the relative risk would be 2.

The design of case-control studies is described in Table II. In a case-control study, the starting point is the disease of interest. Cases of the disease are collected, and control subjects are chosen who are as similar as possible to the case subjects without being affected by the disease. The history of exposure to the suspected agent is obtained for both cases and controls, and the relative risk can then be calculated by dividing the ratio of exposed to nonexposed cases by the corresponding ratio for the controls. In a case-control study, absolute risk cannot be calculated, although it can be estimated if the cases are drawn from a defined population.

Epidemiologic studies of oral contraceptives and cardiovascular disease

Almost all of the studies of the relationship between fatal cardiovascular disease and the pill have been carried out in the United Kingdom, and this article concentrates on the British studies.

Cardiovascular death is a rare event in young women, and thus it takes a long time for a cohort study to include sufficient numbers of relevant deaths to make any calculations of risk. Therefore except for two long-established cohort studies that will be described later, most of the available evidence on oral contraceptives and cardiovascular disease has come from case-control studies.

Table III provides a summary of all the previous British case-control studies of fatal cardiovascular disease.[1-6] The method used in these studies has been very similar, and members of the Oxford Department of Community Medicine and General Practice have been closely involved in all but one. In all the studies, matched controls have been chosen from living women registered with the same general practice as the case subjects. In most of the studies, information was collected at a face-to-face interview with the general practitioner, conducted by a research physician. One study, however, collected the information by correspondence with the general practitioner.

Table IV. Cohort studies of oral contraception

Royal college of general practitioners study[7]
- Started in 1968
- Subjects: 46,000 married women, half of whom used the pill at recruitment (exposed cohort); the other half did not use the pill (control cohort)
- Data on mortality collected from the National Health Service Central Registry; still in progress

Oxford–FPA study[8]
- Started in 1968
- Subjects: 17,000 married women, approximately 10,000 of whom used the pill (exposed cohort); others used diaphragm or intrauterine device (control cohort)
- Data on mortality collected from National Health Service Central Registery; still in progress

In addition to the case-control studies, important information has been provided by two long-running cohort studies (Table IV).[7,8] These two studies have contributed a vast amount of information about both beneficial and harmful side effects of oral contraceptives; between them, the two studies have already resulted in well over 100 original scientific publications. However, there is an important limitation on the extent to which information from these studies can contribute to the current debate on the cardiovascular effects of oral contraceptives. Recruitment into these studies took place during the late 1960s and early 1970s, and as a result, the pills used by these women mostly contained 50 μg of estrogen. These studies give little information on the newer pills, which have lower doses of estrogen.

The principal findings in the various studies to date are summarized in Table V. The most frequent and consistent finding has been an increased risk of myocardial infarction; these studies have shown a relative risk in oral contraceptive users that ranges between

Table V. Relative risk estimates for fatal cardiovascular disease: Oral contraceptive users versus nonusers

	Pulmonary embolism	*Thrombotic stroke*	*Subarachnoid hemorrhage*	*Myocardial infarction*
Case control studies				
Inman and Vessey, 1966	8.3:1	5.7:1	*	1.7:1
Mann et al. 1973	*	*	*	2.8:1
Inman-1976	*	*	1.4:1	*
Adam et al. 1978	*	*	1.2:1	2.2:1
Cohort studies				
Royal College of General Practitioners	*	2.1:1	4.0:1	3.9:1

*Not studied or numbers too small to provide an estimate.

Table VI. Oxford–FPA cohort study

	Cardiovascular mortality	
Total deaths	*Ischemic heart disease (n = 18)*	*Subarachnoid hemorrhage (n = 8)*
Oral contraceptives		
Never used	3	1
Ever used	15	7
Used at time of death	2	0
Smoking at entry into study		
Yes	17	5
No	1	3
Relevant past medical history		
Yes	13	3
No	5	5

Table VII. Oxford–FPA cohort study: Death rates per 100,000 woman years*

	Recency of oral contraceptive use–interval since OCs last used			
Disease	*Never*	*−12*	*13-71*	*72+*
Ischemic heart disease	3.3 (3)	6.7 (3)	9.0 (5)	8.6 (7)
Subarachnoid hemorrhage	1.2 (1)	0.0 (0)	3.1 (2)	7.9 (5)

Rates standardized for age, parity, social class, and smoking habits.
OCs, Oral contraceptives.
*Numbers of deaths in parentheses.

Table VIII. Prevalence of oral contraceptive use in United Kingdom by age group

	Age group (%)			
Yr	*15-19*	*20-29*	*30-39*	*40-49*
1978	22	38	17	5
1983	26	43	15	3
1987	28	45	14	3

around 2 to around 4. Findings from studies of stroke have ranged from a relative risk of 1.4 for subarachnoid hemorrhage to a nearly sixfold increase in risk of thrombotic stroke. Only one study has provided a relative risk for fatal pulmonary embolism; that was a high risk of more than 8, but this study was carried out in the mid-1960s when high-dose preparations dominated the market, and the findings may not be relevant in light of the lower dose preparations in use today.

The findings in these studies of fatal cardiovascular disease, along with those in morbidity studies, have indicated a number of other important associations: (1) Absolute risk increases markedly with age. (2) The risk of myocardial infarction at least is increased by the presence of other risk factors, particularly cigarette smoking. (3) The risks are largely confined to women who use oral contraceptives at the time of death. (4) The risks are influenced little by duration of pill use.

In addition to the studies summarized in Table V, there has recently been a new analysis of mortality in the Oxford-FPA study, which has now accumulated 270,000 woman-years of observation (Table VI). Numbers are still too small for definite conclusions to be drawn, but the most striking finding relates to cigarette smoking. Only one of the deaths from ischemic heart disease occurred in a nonsmoker, and more than half of the cases of fatal subarachnoid hemorrhage were also in smokers. There was also a strong preponderance

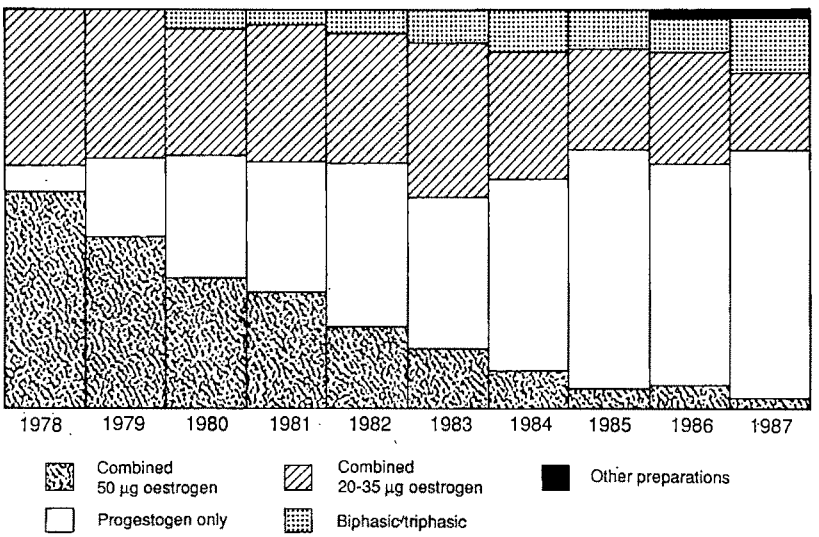


Fig. 1. Percentage distribution of types of oral contraceptives prescribed in women, ages 40 to 54 years.

Table IX. Percentage distribution of types of oral contraceptives prescribed in the United Kingdom since 1963

Type of preparation	*1963*	*1973*	*1983*	*1987*
Combined estrogen/progestogen:				
20-35 μg estrogen	0	3.7	63.3	55.7
50 μg estrogen	34.4	92.3	7.5	2.7
70-80 μg estrogen	17.7	1.0	0	0
100 μg estrogen or more	47.9	1.3	0	0
Sequential OCs	0	0.1	0	0
Biphasic/triphasic OCs	0	0	17.4	32.2
Progestogen-only OCs	0	0.9	7.9	8.8
Other preparations	0	0	3.8	0.7

OCs, Oral contraceptives.

of oral contraceptive users, although only two women (both of whom had ischemic heart disease) used the pill at the time of death.

Table VII shows the death rates per 100,000 woman-years according to how recently oral contraceptives were used. These rates have been standardized to take into account the effect of age, parity, social class, and cigarette smoking. The numbers are small, but it appears that the increased risk is of similar magnitude, even in those women who stopped using the pill at least 6 years before the fatal event. This is an unusual finding but not unique, and clearly, this is an area in which further research is needed.

Changes in use of oral contraceptives

The results discussed so far relate to the use of oral contraceptives during the 1960s and 1970s. However, since then, major changes have occurred both in the dosage prescribed and in the ages of the women using them.

Table VIII, which, along with Table IX and Figs. 1 to 4, is compiled from data supplied by Medical Data Index, shows how the prevalence of oral contraceptive use has changed in different age groups during the past decade. Use by women below the age of 30 years has increased, whereas use by those over 30 years has decreased, with the result that prescriptions of oral contraceptives for women under 30 years have gained an increasingly dominant role in the market. In 1978, 72% of all prescriptions were for women under 30 years; by 1987 it rose to 80%.

There have also been changes in the dosage of the preparations in use. Table IX shows the percentage distribution of the different types of preparations used during the past 25 years. In the 1960s the market was dominated by high-dose combination pills that contained 70 to 100 μg or more of estrogen. By 1973, partly as a result of early work on the relationship between oral contraceptives and cardiovascular disease, there was a massive switch to preparations containing lower doses of estrogen. This trend has continued, with combined pills containing 30 μg or less of estrogen gaining dominance in the market. More recently the new biphasic and triphasic preparations, which deliver lower

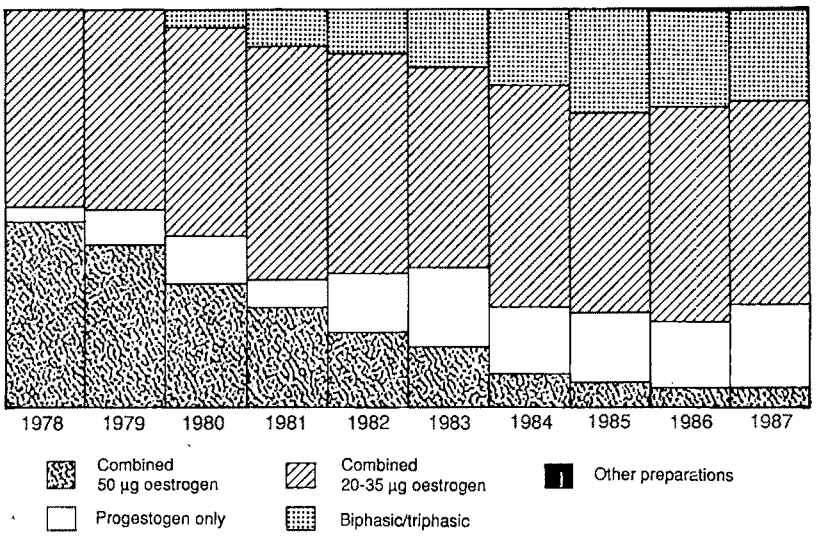


Fig. 2. Percentage distribution of types of oral contraceptives prescribed in women, ages 30 to 39 years.

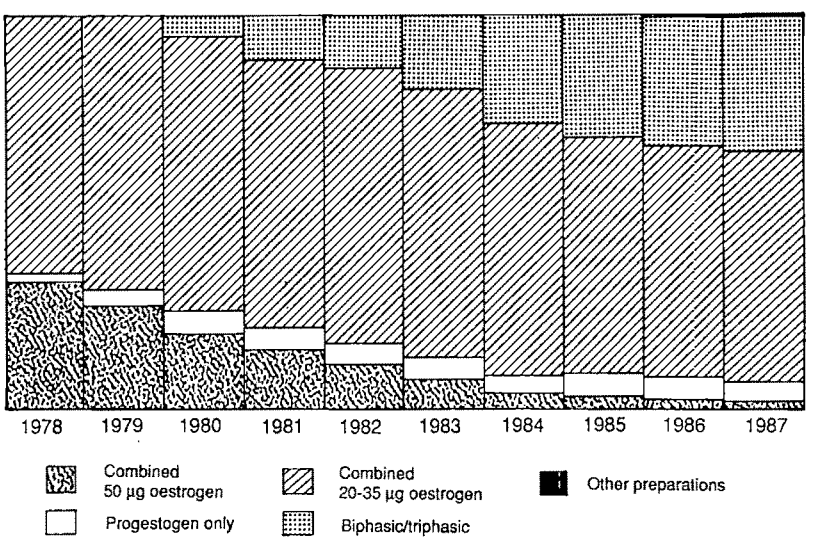


Fig. 3. Percentage distribution of types of oral contraceptives prescribed in women, ages 20 to 29 years.

doses of progestogen over the 28-day cycle, have gained prominence.

Figs. 1 to 4 show how the changes in the dosage of oral contraceptives have affected the age groups differently. In 1978, the older age groups had been much slower to abandon the combined 50 µg pills than younger women, but their use of these preparations declined steadily during the next decade. At the same time, progestogen-only pills, and to a lesser extent for the 30- to 39-year-old age group, biphasic and triphasic pills gained popularity rapidly. In the younger age groups, progestogen-only pills have been used very little, but the biphasic and triphasic pills have shown a remarkably rapid increase in popularity, particularly among the youngest women.

Thus since the major studies on the relationship between oral contraceptives and cardiovascular disease were carried out in the 1960s and 1970s, the pattern of pill use has changed dramatically in ways that might be expected to change the relative risk of cardiovascular disease. Older women, who had the highest absolute risk, use oral contraceptives much less, and those who use them mainly take pills containing either low-dose estrogen or no estrogen at all.

Current case-control study of oral contraceptives

The current case-control study of oral contraceptives and cardiovascular disease began in 1986. All women in England and Wales between 16 and 39 years, who

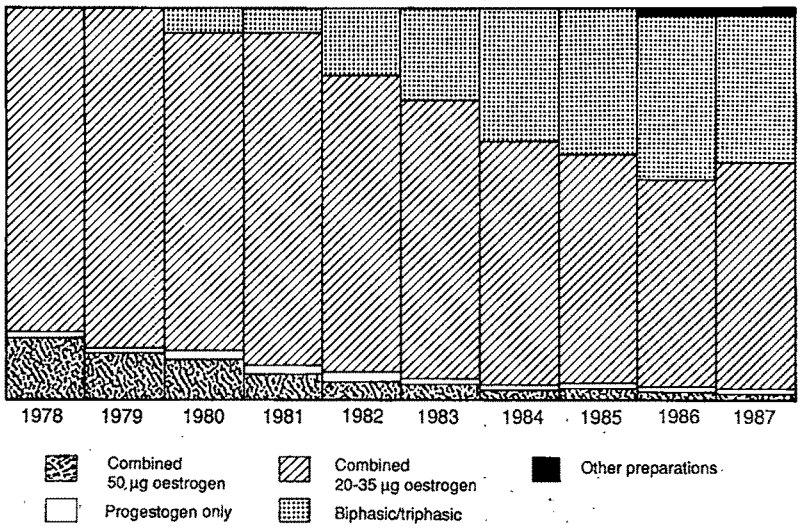


Fig. 4. Percentage distribution of types of oral contraceptives prescribed in women, ages 12 to 19 years.

Table X. Current case-control study of cardiovascular disease in young women: Present position

Total certificates received	934
Investigation continuing	184
Investigation complete	750

died of myocardial infarction, subarachnoid hemorrhage, other stroke, and pulmonary embolism, and/or deep vein thrombosis, have been included in the study.

The design of this study is very similar to that of the case-control studies previously described. The data are collected by medical officers, who carry out interviews with the general practitioners of the cases. There are two control subjects per case, matched by 5-year age group and marital status, and selected from the living women registered with the same general practitioner.

This study is still in progress, and there are 184 patients in whom the investigation is not yet complete (Table X). However, we are in a position to report some very preliminary results of the investigation of the other 750 cases.

Table XI shows the reasons why 231 patients have been excluded from the study. Ten were excluded because they were not residents of England and Wales. We were unable to continue the investigation of another 85 subjects either because the notes were lost, the general practitioner could not be identified, or the general practitioner declined to cooperate. In addition, there were 55 patients in whom we did not feel that there was sufficient medical evidence to ascertain the cause of death. Pregnant patients and those already gravely ill with another disease were also excluded because it was very unlikely that they took oral contraceptives.

Table XI. Current case-control study of cardiovascular disease in young women: Reasons for exclusion of cases

Not resident of England and Wales	10
Medical records mislaid	40
Unable to confirm diagnosis	55
Pregnant or up to 8 wk post partum	49
Case gravely ill with other disease	17
Case institutionalized	22
General practitioner not traced	10
General practitioner refused interview	35

Table XII. Current case-control study of cardiovascular disease in young women: Completed cases by diagnostic group

Myocardial infarction (ICD 410)	130
Subarachnoid hemorrhage (ICD 430)	237
Other strokes (IDC 431-438)	110
Venous thromboembolism (ICD 415.1, 451-453)	42

Patients who were institutionalized were excluded for the same reason.

Thus the results relate to 519 completed cases, but mainly to the 130 patients who died of myocardial infarction and the 237 who died of subarachnoid hemorrhage, since there are not enough deaths in either of the other two categories for conclusions to be drawn as yet (Table XII).

Age distribution by cause of death is shown in Table XIII. There is a strong effect of age on myocardial infarction, a smaller effect for both categories of stroke, and apparently no effect of age on the risk of fatal venous thromboembolism.

The use of female hormones, mainly for contracep-

Table XIII. Current case-control study of cardiovascular disease in young women: Distribution of cases by diagnosis and age group

Diagnosis	*Age (yr)*				
	16-19	*20-24*	*25-29*	*30-34*	*35-39*
MI	0 (0)	2 (2)	10 (8)	31 (24)	87 (67)
SAH	8 (3)	22 (9)	38 (16)	56 (24)	113 (48)
OS	4 (4)	14 (13)	14 (13)	27 (25)	51 (46)
VT	8 (19)	10 (24)	5 (12)	8 (19)	11 (26)

MI, Myocardial infarction; *SAH*, subarachnoid hemorrhage; *OS*, other strokes; *VT*, venous thromboembolism.

tive purposes but occasionally for other reasons such as treatment of menorrhagia or endometriosis, was more prevalent among patients with myocardial infarction than among matched controls. Twenty-four percent of the cases used female hormones at the time of death compared with 19% of control subjects, giving a statistically significant relative risk of 1.8. In accordance with the changes in pill dosage and use previously discussed, the relative risk is smaller than that found in most of the earlier studies.

Collecting data about smoking habits from general practice records has in the past been a thankless task. However, there is an increasing awareness among general practitioners of the need to record this information, and in this study it is possible to provide estimates of the relative risk associated with smoking. These data should be interpreted with caution, since it is likely that there is a greater tendency for medical practitioners to record a positive smoking history rather than the absence of a smoking history, and smoking histories were available for a larger percentage of the case subjects than the controls. Nevertheless, the risk of myocardial infarction in women known to be smokers was increased nearly 12-fold (95% confidence intervals, 6 to 23), and it seems reasonable to suppose that there is a real increase in risk of considerable size.

Women already at risk of having a heart attack might well be strongly recommended not to use oral contraceptives or smoke. Inclusion of these women may thus reduce the number of exposed cases and relative risk estimates. About one third of the cases and just 3% of the control subjects had one of the recognized risk factors for myocardial infarction. After cases and controls with recognized risk factors were excluded, the relative risk of both female hormone use and smoking increased. The risk in women who both smoked and used oral contraceptives was increased more than 50-fold.

The risk of subarachnoid hemorrhage in women using oral contraceptives was small. There was a relative risk of 1.4 (95% confidence intervals, 1.0 to 2.0) for women who had ever used female hormones compared with those who had never used them. This risk is similar to that noted in the two previous case-control studies. In addition, there was a risk of subarachnoid hemorrhage associated with cigarette smoking. The relative risk was 3.1 in current smokers compared with women who had never smoked. This compared closely with the relative risk for subarachnoid hemorrhage of 2.9 in current smokers, which was estimated in a recent meta-analysis.[9]

About a fourth of the cases had recognized risk factors for subarachnoid hemorrhage compared with just 3% of the control subjects. However, the exclusion of these women made little difference in relative risk estimates. None of the risk estimates for other forms of stroke or for venous thromboembolism reached statistical significance, but the numbers of cases are small.

In conclusion, changes in the use of oral contraceptives have been described. These changes have led to a considerable reduction in the use of estrogen-containing preparations among women in their thirties. Some very preliminary and incomplete results from a new case-control study still in progress have been described. It does appear that the changes in oral contraceptive use may have had the effect of reducing the relative risk of myocardial infarction for pill users, although there appears to be little change in the (already small) risk of subarachnoid hemorrhage. The most striking finding relates to smoking. Smoking is a major risk factor for both diseases and is a particularly strong risk factor for myocardial infarction. The risk of myocardial infarction in women who both smoke and use oral contraceptives is estimated to be increased more than 50-fold.

We are grateful for the data on oral contraceptive prescriptions in England and Wales, which was kindly supplied by Medical Data Index (Intercontinental Medical Statistics, Ltd.).

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Cardiovascular death among women under 40 years of age using low-estrogen oral contraceptives and intrauterine devices in Finland from 1975 to 1984

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From 1975 to 1984, there were 1,585,000 women-years of oral contraceptive use and 1,975,000 women-years of copper-bearing intrauterine device use in Finland. During this 10-year period, 20 women between 15 and 39 years of age died of pulmonary embolism, 41 of coronary heart disease, and 311 of intracranial hemorrhage. The diagnoses were confirmed in 89% at necropsy examination. The contraceptive method used by patients was determined in 84% by means of inquiry sent to family planning clinics. Among the 20 patients who died of pulmonary embolism, four died while taking the pill, which gives a relative risk of 1.2 (95% confidence limits, 0.37 to 3.62; $p = 0.78$). The corresponding values for death from myocardial infarction and intracranial hemorrhage were 0.19 (95% confidence limits, 0.05 to 0.70; $p = 0.01$) and 0.36 (95% confidence limits, 0.18 to 0.70; $p = 0.03$), respectively. None among the copper intrauterine device users under the age of 40 years died of pulmonary embolism during 1,383,000 women-years of intrauterine device use. The relative risk of death from intracranial hemorrhage among intrauterine device users was 1.18 (95% confidence limits, 0.70 to 1.99, $p = 0.25$). (Am J Obstet Gynecol 1990;163:281-4.)

Key words: Low-estrogen oral contraceptives, thromboembolism, cerebral vascular complications, coronary heart disease, intrauterine device

In 1970, a new liberal abortion law was passed in Finland, and as a result, the number of legal abortions increased in 3 years to 20/1000 women of fertile age (Fig. 1). After the reorganization of the family planning clinics in 1973, the number of legal abortions in the next 8 years decreased to 12 per 1000 per year. Since the early 1970s, the national policy has been favorable for accepting new contraceptive methods (Table I). Copper intrauterine devices were registered in 1972 and became the most popular contraceptive method in the next 5 years in Finland. It is calculated that these two method are used by 45% to 50% of women who need contraception. Intrauterine devices are recommended mainly to parous women over 30 years of age. Oral contraceptives are contraindicated for women over 40 years, and those over 30 years of age who also smoke are recommended to change to another method. Because the increase in thromboembolism associated with the use of high-estrogen oral contraceptives they were withdrawn from the market 1974.[1] Subsequently, in 1974, the first preparations containing 30 μg of ethinyl estradiol were registered, and according to the sales statistics, their use increased in 10 years up to 82% of oral contraceptive use. Since the cause of death is confirmed in about 90% of cases at necropsy examination in Finland, the diagnostic certainty is high, and it seemed appropriate to study the fatal cardiovascular

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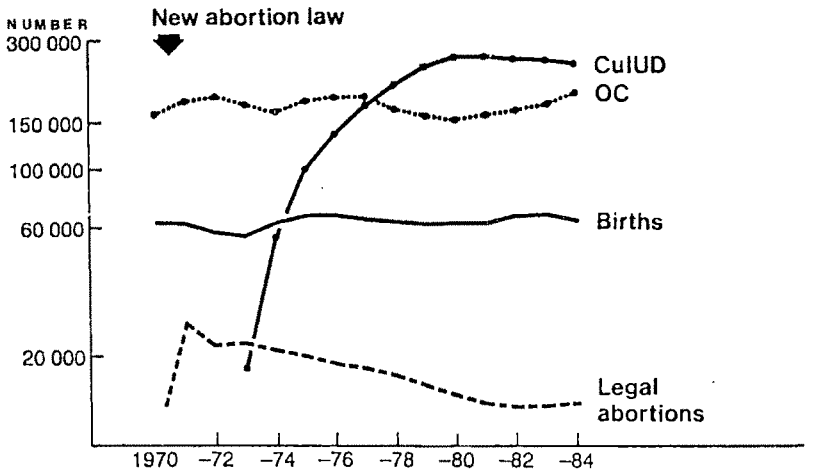


Fig. 1. Births, legal abortions, oral contraceptive users *(OC)*, and users of copper-bearing intrauterine device *(CuIUD)* in Finland from 1970 to 1984.

Table I. Family planning in Finland (1970 to 1984)

1970	New liberal abortion law was passed
1971	Progestin-only pills were registered
1972	Copper-bearing intrauterine devices were registered
1974	Low-estrogen oral contraceptives were registered
1974	Withdrawal of high-estrogen oral contraceptives
1981	Triphasic oral contraceptives and a combination of ethinyl estradiol/desogestrel (30/150) were registered
1984	Levonorgestrel implants (Norplant) were registered

complications among oral contraceptive and intrauterine device users.

Material and methods

Data from the Central Bureau of Statistics were used to count the annual number of women in different age groups and the number of deliveries per year. From 1975 to 1984, the number of women between 15 and 39 years of age has remained constant, between 926,000 and 941,000 in each year (mean, 935,000). The total number of oral contraceptive users and the share of various preparations can be calculated from the national sales statistics. The number of copper intrauterine device users per year can be estimated approximately by using a biostatistical linear model. This requires that the effective lifetime (3 or 5 years), continuation rate during the lifetime, and the number of insertions per year of different copper intrauterine devices are known. During this period, there has been a total of 1,585,000 women-years of oral contraceptive use among all Finnish women and 1,383,000 women-years of intrauterine device use among women under 40 years of age.

Death certificates for women, ages 15 to 39 years, who died of diseases of the circulatory system from 1975 to 1984 were obtained from the Central Bureau of Statistics. The ICD codes (1969 revision of the International Classification of Diseases) and diagnoses and the number of cases are presented in Table II.

Twenty deaths were from pulmonary embolism, 41 from coronary heart disease, and 311 from cerebrovascular diseases. Autopsies were performed in 89% of the cases, and in the rest the diagnoses were based on history, physical signs, neurosurgery, and results of special investigations (computerized tomography, angiography, electrocardiography, spinal fluid, etc.). The case records of those who died in hospitals were obtained, but these were inaccurate to determine the contraceptive method used by the patient. Therefore a request was sent to the residence health centers and family planning clinics. Because of the large number of cerebral arterial complications, only cases from 1980, 1982, and 1984 were included. All inquiries were returned to the Finnish National Board of Health.

In the same period there were 647,000 live births and 40 pregnancy-related deaths (6.18/100,000 births/yr) in Finland. Of these five died of pulmonary embolism (two were complications after cesarean section), one of coronary heart disease, and six of intracranial hemorrhage. The annual number of deliveries and pregnancy-related cardiovascular deaths is subtracted from controls in the statistical analysis (Table III).

The contraceptive method was established in 17 of the 20 patients with pulmonary embolism, in 36 of the 41 cases with coronary heart disease, and in 83 of the 108 patients with intracranial hemorrhage (Table III). Intrauterine devices were found during autopsies. Sta-

Table II. Death certificates of women between 15 and 39 years of age between 1975 and 1984 in Finland

ICD code	*Diagnoses*	*No. of cases*
410-413	Myocardial infarction	41
450	Pulmonary embolism	20
430	Subarachnoid hemorrhage and	311
431	intracerebral hemorrhage	
433	Cerebral thrombosis	0
434	Cerebral thromboembolism	0

ICD, International Classification of Diseases.

Table III. Contraceptive method by cause of death

Cause	*Total No. of cases*	*Pregnancy related*	*Established contraceptive method*	
			OC users	*IUD users*
Pulmonary embolism	20	5	4	0
CHD	41	1	2	5
Intracranial hemorrhage	108	6	9	20

OC, Oral contraceptive; *IUD,* intrauterine device; *CHD,* coronary heart disease.

Table IV. Cardiovascular deaths among oral contraceptive and intrauterine device users in Finland from 1975 to 1984

	OC users	*Nonusers*	*RR*	*p Value*	*95% CL*	*IUD users*	*Nonusers*	*RR*	*p Value*	*95% CL*
Deaths from pulmonary embolism	4	11	1.2	0.78	0.37-3.68	0	11	0	0.07	0
Women-years	1,585,000	5,107,000				1,383,000	5,107,000			
Deaths from CHD	2	33	0.2	0.01	0.05-0.70	5	33	0.6	0.2	0.25-1.69
Women-years	1,585,000	5,107,000				1,383,000	5,107,000			
Deaths from intracranial hemorrhage	9	73	0.7	0.03	0.18-0.90	20	73	1.18	0.25	0.70-1.99
Women-years (1980, 1982, 1984)	485,000	1,428,000				490,000	1,428,000			

RR, Relative risk; *CL,* confidence limits.

tistical significance has been calculated by exact one-sided χ^2 test, and 95% confidence limits for relative risks are test-based calculations.[2]

Results

Among the 20 patients who died of pulmonary embolism, seven women had no predisposing factors for pulmonary embolism; four patients were current oral contraceptive users, but none used an intrauterine device. The contraceptive method could not be determined in three cases. The relative risk of death from pulmonary embolism was 1.2 (95% confidence interval, 0.37 to 3.62; $p = 0.78$) for oral contraceptive users (Table IV).

Among the 41 patients who died of coronary heart disease, the contraceptive method used was established in 36 subjects; only two women were current oral contraceptive users, and five were intrauterine device users. The relative risk of death from myocardial infarction was 0.19 (95% confidence interval, 0.05 to 0.70; $p = 0.01$), for oral contraceptive users and 0.66 for intrauterine device users (95% confidence interval, 0.25 to 1.69; $p = 0.2$).

All 108 patients who died of intracranial vascular disease had intracranial hemorrhage that was caused by a rupture of an aneurysm (60 patients). None had cerebral thromboembolism. Among patients who died of intracranial hemorrhage, the contraceptive method was determined in 84 cases. Nine women were current oral contraceptive users, which gives a relative risk of 0.36 (95% confidence interval, 0.18 to 0.70; $p = 0.03$). Twenty women (23.8%) were intrauterine device users. The relative risk of death from intracranial hemorrhage for intrauterine device users was 1.18 (95% confidence interval, 0.70 to 1.99; $p = 0.25$). Hypertension was present in 18% of patients who died of intracranial hemorrhage, and the mean age in this group was higher (34.6 ± 4.1 years) than that (31.4 ± 6.6 years) in patients with pulmonary embolism.

Comment

The decrease in estrogen content in oral contraceptives resulted in striking decreases in thromboembolic complications in Sweden, but the incidence of the most serious complication, pulmonary embolism, and that of arterial complictions did not decrease.[3] The results obtained in our study suggest that there may be an increased risk of death from pulmonary embolism among low-estrogen (≤50 μg of ethinyl estradiol) users. None of the four oral contraceptive users who died of pul-

monary embolism had any evident predisposing factors for pulmonary embolism as was the case with the three patients whose contraceptive method could not be established. These three patients were not intrauterine device users, but may have used oral contraceptives. It is possible that these four healthy oral contraceptive users might have had some deficiency in the coagulation system, such as low levels of antithrombin III, protein C, or protein S.

The incidence of death from coronary heart disease among oral contraceptive users was very low. This is mainly because coronary heart disease and the presence of its risk factors have greatly influenced the contraceptive choice, decreasing the relative risk of oral contraceptive users.[4]

Cerebral vascular complications are difficult to predict. The mean age of this group was higher than that of women who died of pulmonary embolism. We found hypertension in 18% of patients who died of intracranial hemorrhage, which was caused in 60% by a rupture of an aneurysm. Both hypertension and age influence the contraceptive choice and decrease the relative risk of oral contraceptive users and could increase the risk among intrauterine device users.

An increase in the use of copper intrauterine devices occurred from 1975 to 1979 in Finland, but the number of users remained constant between 1980 and 1984. The continuation rates of different copper intrauterine devices among Finnish women are known and could be used in the calculations of total number of users per year.[5]

The advantage of this study is that the level of diagnostic certainty is high; 89% of the diagnoses were confirmed at necropsy with the remainder made by sophisticated clinical methods. This study includes all deaths from cardiovascular causes during a 10-year period among all Finnish women between 15 and 39 years of age who are potential oral contraceptive users. Bias may be caused by the fact that we were unable to determine with certainty all oral contraceptive users, whereas the use of intrauterine devices was confirmed at necropsy examination. However, there was an excellent correlation between the number of intrauterine devices found at necropsy and that reported by the family planning clinics, which suggests that the reported number of oral contraceptive users is also near correct. Another bias is caused by the fact that the mean age of oral contraceptive users is lower than that of nonusers or intrauterine device users because many physicians prefer to recommend intrauterine devices instead of oral contraceptives for women over 35 years.

These results suggest that modern low-estrogen oral contraceptives are very safe for healthy women under 40 years of age but may still have some influence on the coagulation system, causing an excess risk of one death from pulmonary embolism per 1 million users per year. The risk of death from myocardial infarction seems to be smaller than in control subjects, owing to the careful exclusion of patients with risk factors for coronary heart disease, such as hypertonia, smoking after the age of 30 to 35 years, family history of cardiovascular diseases, and hypercholesterolemia. The proposed protective effect of oral contraceptives against cardiovascular disease could not be confirmed in this study.

The risk of intracranial hemorrhage, which in 60% of patients was caused by a rupture of an aneurysm, does not seem to be associated with the use of the pill, which probably is mainly accounted for by measuring the blood pressure at regular intervals and exclusion of patients with headache from oral contraceptive users. With the modern contraceptive methods, the lowest possible risk is reached through education of medical personnel, liberal use of alternative contraceptive methods, and exclusion of patient with risk factors, for cardiovascular diseases, such as patients with family history and smoking after the age of 35 years from oral contraceptive use.

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Past use of oral contraceptives and cardiovascular disease: A meta-analysis in the context of the Nurses' Health Study

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We examined the effects of past use of oral contraceptives on risks of cardiovascular diseases prospectively in the Nurses' Health Study cohort. The 119,061 participants were 30 to 55 years old and free of coronary disease or stroke in 1976. They provided information on biennial questionnaires and were followed for 8 years. There were 380 nonfatal myocardial infarctions and 105 deaths from coronary disease, 282 strokes, and 48 other cardiovascular deaths. We observed virtually no differences in the rates of various cardiovascular diseases between never and past users of oral contraceptives, regardless of duration of use or time since last use. For major coronary disease, the relative risk was 0.8 (95% confidence intervals, 0.6 to 1.0). A quantitative meta-analysis of 13 studies yielded an estimated relative risk of 1.01 (95% confidence intervals, 0.91 to 1.13) for coronary heart disease. Past use of oral contraceptives has little or no impact on risks of subsequent cardiovascular diseases. (AM J OBSTET GYNECOL 1990;163:285-91.)

Key words: Oral contraceptives, myocardial infarction, cardiovascular disease, stroke, women

The risk of myocardial infarction is increased among current users of oral contraceptives, especially cigarette smokers.[1-14] However, whether this excess risk persists among past users is unclear. Current oral contraceptive use can adversely affect several coronary risk factors, including raising levels of the atherogenic low-density lipoprotein and lower high-density lipoprotein, which is associated with reduced atherosclerosis.[15-17] Oral contraceptives can also impair glucose tolerance[16] and raise blood pressure.[18-21] Despite these deleterious changes in risk factors, most, but not all, studies have failed to observe an increase in risk of cardiovascular disease among women who have stopped using oral contraceptives.[1-5, 12, 22-26] One large case-control study has been widely interpreted as showing an increased risk of myocardial infarction among past users; the magnitude appeared to increase with a longer duration of use.[10] Even a modest excess risk among past users could be important because those women will be older than current users and thus have higher absolute rates of cardiovascular disease. If past use increased this rate by even a small amount, the absolute excess risk attributable to oral contraceptives could be large.

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In this article we review the pertinent literature, provide additional information from the Nurses' Health Study, the largest prospective investigation to date of the effect of past use of oral contraceptives on risk of cardiovascular diseases,[24] and perform a quantitative meta-analysis on all available data on this question. We conclude that past use of oral contraceptives is not associated with an excess risk of cardiovascular events.

Methods

The Nurses' Health Study cohort was established in 1976 when 121,700 female nurses 30 to 55 years of age completed a mailed questionnaire that included items on known or suspected risk factors for cancer[27] and coronary heart disease.[28] Follow-up questionnaires are mailed every 2 years to update information on risk factors and to identify newly diagnosed illnesses. The 1976 questionnaire included a complete history of all intervals of oral contraceptive use, and this information was brought up to date by follow-up questionnaires sent in 1978, 1980, and 1982. We defined current oral contraceptive use as use within 1 month of the date of return of the questionnaire. Past use was defined as use that ceased at least 1 month before the return of the questionnaire. Total duration of use was calculated by adding together the durations of all intervals of use for each woman. We also determined the duration since last use of oral contraceptives.

The participating nurses who reported a nonfatal myocardial infarction or stroke were asked for permission to review the medical records. We applied the

World Health Organization criteria for diagnosis of myocardial infarction; these require symptoms plus either enzyme elevations or diagnostic electrocardiographic changes.[29] We used the criteria of the National Survey of Stroke[30] to confirm the diagnosis of stroke. Reported new strokes that required hospitalization and for which additional confirmatory information was obtained (typically from an interview), but for which no medical records were available, were considered probable.

Fatal cases were identified through reports by next of kin and by a systematic search of the National Death Index.[31] Whenever possible, we reviewed the relevant medical records. The category of death caused by coronary disease included fatal myocardial infarctions (confirmed by records or autopsy), or when coronary disease was listed as the underlying cause of death on the death certificate without another plausible cause, and the woman was known to have had coronary disease before her death. In no case did we rely solely on the cause given on the death certificate to confirm a fatal coronary event. Deaths caused by stroke were confirmed on the basis of medical records, autopsy, or death certificate.

The category of fatal cardiovascular disease included fatal coronary heart disease and stroke, as well as sudden death and deaths for which coronary disease was listed as the cause and no more plausible cause could be assigned but for which confirmation was lacking; these latter categories were designated presumed coronary deaths. The category of major cardiovascular disease included fatal cardiovascular disease and nonfatal myocardial infarction and stroke.

This analysis was based on 119,061 women who were free of diagnosed coronary disease in 1976 and who provided information on oral contraceptive use on the baseline questionnaire. Person-time was allocated according to the 1976 exposure variables and updated on subsequent follow-up questionnaires, until death or a nonfatal endpoint was reached, or until the end of the follow-up period, May 31, 1984. We calculated relative risks, which were defined as the ratio of the incidence of cardiovascular end points among past oral contraceptive users compared with never users. Age-specific and age-adjusted rates were calculated using 5-year age categories, and 95% confidence intervals were calculated.[32] We used the Mantel test to evaluate linear trend[32] and proportional hazards models[33] to simultaneously adjust for multiple risk factors. Further details of the methods have been published elsewhere.[24]

Through computer searches and a detailed review of references from the literature, we identified 13 studies with quantitative data on the effect of past use of oral contraceptives on risk of coronary disease. To obtain a quantitative overview of results from different studies, we calculated a weighted average of the estimated relative risks associated with past use of oral contraceptives. Each study's relative risk was given a weight that corresponded to its precision (i.e., the inverse of an estimate of the variance). An estimate of the variance was derived by calculating the standard error from the confidence interval from each study. Thus larger studies (with more precise estimates, i.e., narrower confidence limits) were given greater weight than smaller ones.[34] For studies in which no point estimate or confidence intervals were given, we calculated these from data published in the papers. We made no attempt to weight studies by the estimated quality of information based on study design, potential bias, or other factors.

A separate meta-analysis included only the cohort studies. Five of the 13 studies provided estimates that were adjusted for confounding factors. We estimated the effect of unadjusted confounding in the remaining studies by taking a weighted average (weighted by the inverse of the variance of each study) of the ratio of the adjusted and unadjusted point estimates, and applied it to studies that provided only age-adjusted results. This permitted a meta-analysis that attempted to take into account the effects of confounding variables, so far as this is possible in nonrandomized studies. These meta-analyses make the assumption that each of the studies was estimating the same underlying parameter. Also, the adjustment for confounding makes the assumption that the distribution of confounders was the same in all studies. We recognize that these assumptions are not strictly met, because the studies were conducted in different populations. Despite these and other limitations in the meta-analysis of observational data,[34] this approach can provide a guide about the strength of the evidence, especially since individual studies are so consistent.

Results

Nurses' Health Study. In 1976, 49,269 women were past users of oral contraceptives, 62,718 participants had never used them, and 7074 were current users. During follow-up, nearly all current users in 1976 had become past users. Because use of oral contraceptives became widespread only in the mid-1960s, many of the participants were beyond the age at which their use was usually initiated. Thus never users tended to be older than past users; current users tended to be younger than past users (Table I). In addition, past users tended to be less obese, had more hypertension, and tended to smoke more than never users.

Follow-up of the cohort for fatal outcomes was more than 98% complete; for nonfatal events, the follow-up was 92% complete. In all, there were 380 documented nonfatal myocardial infarctions, 282 strokes (77 fatal

Table I. Characteristics of current, past, and never users of oral contraceptives among 119,061 Nurses' Health Study participants, 1976

	Oral contraceptive use		
	Never use	*Current use*	*Past use*
No. in 1976	62,718	7,074	49,269
% of participants in 1976	52.7	5.9	41.4
% by age in 1976			
30-34	8.0	41.3	28.8
35-39	13.6	25.3	26.6
40-44	20.8	19.0	21.4
45-49	25.6	10.9	13.8
50-55	32.0	3.4	9.4
Total person-years of follow-up (1976-1984)	484,096	22,376	415,488
Risk factor: % with potential risk factor*			
High cholesterol	3.4	4.1	4.1
Parental MI <60 yr old	13.9	13.2	14.4
Hypertension	11.8	12.0	16.4
Diabetes	1.9	1.0	1.9
Postmenopausal hormone use	23.4	—	31.9
Current smoking	32.5	35.8	34.2
Quetelet index >29 kg/m^2	12.4	8.0	9.9

MI, Myocardial infarction.

*The percentages within each risk factor category have been directly age standardized by 5-year age categories to the distribution of ages among never users.

Table II. Age-specific relative risks of major cardiovascular diseases among past users of oral contraceptives compared with those who never used oral contraceptives in the Nurses' Health Study, 1976-1984*

Rate/100,000 person-years			*Cases of major CVD*				
Age (yr)	*Past OC*	*Never OC*	*Past OC*	*Never OC*	*RR*	*95% CI*	*p*
30-34	20.1	11.7	11	2	1.7	0.4-7.6	0.5
35-39	12.4	18.6	14	9	0.7	0.3-1.5	0.3
40-44	38.1	39.2	39	32	1.0	0.6-1.6	0.9
45-49	88.5	80.7	66	89	1.1	0.8-1.5	0.6
50-54	144.5	150.1	71	202	1.0	0.7-1.3	0.8
55-59	172.9	227.1	35	190	0.8	0.5-1.1	0.1
60-64	421.9	389.3	6	31	1.1	0.5-2.6	0.9

CVD, Cardiovascular disease; *RR*, relative risk; *CI*, confidence interval; *OC*, oral contraceptive.

*Major cardiovascular disease includes fatal and nonfatal stroke, deaths from coronary heart disease, and nonfatal myocardial infarction.

and 205 nonfatal), and 105 deaths from coronary heart disease. In addition, there were 24 sudden deaths and 24 presumed coronary deaths, for a total of 230 cardiovascular deaths.

There was inadequate information to evaluate the risks associated with current oral contraceptive use in detail. However, the risk of major coronary disease (nonfatal myocardial infarction and fatal coronary disease) was significantly elevated in current users; the age-adjusted relative risk was 2.5 (95% confidence interval, 1.3 to 4.9). Seven of the 10 cases occurred among current cigarette smokers.

Because of the differences in age distribution between past and never users of oral contraceptives, all the relative risks are age adjusted. Within each 5-year age category, we observed no evidence of any increase in risk among past oral contraceptive users (Table II). Similar findings were observed in age-specific analyses for each of the various categories of cardiovascular disease.

The age-adjusted results were similar: we found no overall increase in the risk of cardiovascular disease among past users of oral contraceptives (Table III). For all major cardiovascular disease combined, the age-adjusted relative risk was 0.95 (0.81 to 1.11). For major coronary disease it was 0.91 (95% confidence interval, 0.74 to 1.12), and for fatal cardiovascular disease, 0.98 (95% confidence interval, 0.73 to 1.32). When we adjusted for other risk factors using proportional hazards models, the multivariate relative risks decreased slightly (Table III).

Table III also shows the risk estimates by duration of past oral contraceptive use. There was no evidence of a trend toward an increase in risk with an increase in duration of use. Similarly, there was no evidence of a trend in change in risk with increasing duration since last use.[24] The risk was near the null value even for women who recently stopped using oral contraceptives.

Slone et al.[10] observed that premenopausal women, ages 40 to 49, had an age-adjusted and risk factor–adjusted relative risk of 1.6 (95% confidence interval, 1.1 to 2.5) for 5 to 9 years of prior use and 2.5 (95% confidence interval, 1.5 to 4.1) for 10 or more years of use. We specifically examined this group and found no evidence to suggest an increase in risk. Among premenopausal women, ages 40 to 49 years, with 5 to 10 years of prior use, the relative risk for major coronary disease was 0.6 (95% confidence interval, 0.2 to 1.4) and for women with more than 10 years of prior use, it was 0.5 (95% confidence interval, 0.1 to 2.1).

Meta-Analysis of past use of oral contraceptives and cardiovascular disease. Reports from most but not all studies of past use of oral contraceptives and risk of coronary disease have also indicated no increase in risk. The positive findings of Slone et al. were limited to a specific subgroup; no excess risk was found in postmenopausal former users or among past users under age 40 years (Table IV). Overall, after adjustment for

Table III. Age-adjusted relative risks of cardiovascular disease among past users of oral contraceptives by duration of use and overall compared with never users in the Nurses' Health Study, 1976 to 1984

	Category of cardiovascular disease							
	Major coronary disease		*Total stroke*		*Fatal cardiovascular disease*		*Major cardiovascular disease*	
Duration of use (mo)	*Cases (n)*	*RR (95% CI)*	*Cases (n)*	*RR (95% CI)*	*Cases (n)*	*RR (95% CI)*	*Cases (n)*	*RR (95% CI)*
Never	339	1.0 (referent)	185	1.0 (referent)	156	1.0 (referent)	555	1.0 (referent)
1-11	45	1.0 (0.7-1.4)	23	0.8 (0.5-1.3)	25	1.1 (0.7-1.7)	74	1.0 (0.8-1.2)
12-35	32	1.0 (0.7-1.4)	16	0.8 (0.5-1.3)	10	0.5 (0.3-1.1)	50	0.9 (0.7-1.2)
36-59	20	1.0 (0.6-1.7)	15	1.1 (0.6-2.0)	7	0.7 (0.3-1.5)	37	1.1 (0.8-1.5)
60-119	25	0.8 (0.5-1.2)	28	1.4 (0.9-2.1)	16	1.0 (0.6-1.7)	53	1.0 (0.7-1.3)
120+	10	0.7 (0.4-1.2)	11	1.3 (0.7-2.3)	9	1.3 (0.6-2.5)	22	0.9 (0.6-1.3)
X trend* (*p* value)		−1.51 (0.13)		1.36 (0.17)		−0.18 (0.86)		−0.61 (0.54)
Overall† age-adjusted relative risk	136	0.91 (0.74-1.12)	94	1.01 (0.78-1.32)	70	0.98 (0.73-1.32)	242	0.95 (0.81-1.11)
Multivariate†‡ relative risk		0.80 (0.64-0.99)		0.96 (0.74-1.25)		0.90 (0.67-1.21)		0.85 (0.72-1.00)

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*Test for trend includes never users.

†Includes those for whom the duration of past use was unknown.

‡Potential risk factors included in the proportional hazards model were a parental history of infarction before age 60 years (yes or no), menopausal status and hormone use (premenopausal, postmenopausal and current hormone user, postmenopausal without current hormone use), time period (1976 to 1978, 1978 to 1980, 1980 to 1982, and 1982 to 1984), smoking status (current [at three levels of intensity], past, and never), hypertension (yes or no), diabetes (yes or no), high cholesterol (yes or no), age (five categories), and Quetelet index (five quintiles).

Table IV. Age-adjusted relative risks and 95% confidence intervals[10]

	Yr of past use of oral contraceptives		
Subgroup	*<5*	*5-9*	*10+*
Premenopausal			
Age 25-39 yr	0.8 (0.5-1.4)	0.8 (0.4-1.8)	1.5 (0.4-6.0)
Age 40-49 yr	1.0 (0.8-1.4)	1.6 (1.1-2.5)	2.5 (1.5-4.1)
Postmenopausal		0.8*	
Overall age-adjusted relative risk, all durations: 1.2 (95% CI, 0.9-1.4)			
Overall multivariate† relative risk, all durations: 1.1 (95% CI, 0.9-1.4)			

CI; Confidence interval.

*Combined for 5 or more years duration of prior use; no confidence interval was given.

†Adjusted for age and a wide array of coronary risk factors.

a variety of coronary risk factors, no increase in the risk of myocardial infarction among past users was observed: the relative risk was 1.1 (95% confidence interval, 0.9 to 1.4).

These essentially null findings are consistent with nearly all previous studies addressing this issue (Table V). Preliminary reports[12] from studies listed in Table V have not been included if the data are subsumed in subsequent reports to avoid duplicate counting of the same data. Data from the Oxford Family Planning Study[35] are not included because age-adjusted data, specifically for past users, were not given. In that study past users appeared to have a slight, nonsignificantly elevated risk, but there were only 13 exposed cases, so it is unlikely that their inclusion would have materially influenced the meta-analysis. Of the 13 studies summarized in Table V, none show a significant increase in risk, and all but one report estimates close to the null value. Only one, the study by Jick et al.,[36] has a substantially (although not significantly) elevated point estimate above 1.0. This study had only four exposed cases and only two unexposed cases to serve as the reference category. Moreover, only 15% of the potential patients were enrolled, suggesting the likely occurrence of selection bias.

Most of the studies did not adjust for other coronary risk factors. In general, past users appeared to have a slightly higher baseline risk than did never users. Thus multivariate adjustment tended to slightly reduce the relative risk associated with past use of oral contraceptives. Table V shows that in four of the five studies that calculated both age-adjusted and multivariate relative risks, the adjustment for other risk factors further attenuated the relative risk.

The findings are remarkably consistent in showing little or no effect of past use of oral contraceptives on risk of myocardial infarction. The meta-analysis of all 13 studies, which used both adjusted (where available)

Table V. Published reports on past use of oral contraceptives and risk of myocardial infarction

Study	*Design*	*Exposed cases*	*RR, 95% CI*	*Unadjusted RR*
Mann et al., 1975[1]	C/control	6 NF MI	1.1 (0.4-3.0)*	
Mann 1975, 1976[2, 3]	C/control	18F MI	1.1 (0.6-2.0)*†	
Jick et al., 1978[36]	C/control	4 NF MI	3.6 (0.6-20.6)*	
Petitti et al., 1979[23]	Prospective	6 F + NF MI	0.8 (0.3-2.1)*	
Shapiro et al., 1979[4]	C/control	86 NF MI	1.2 (0.8-1.7)	
Rosenberg et al., 1980[5]	C/control	29 NF MI	0.9 (0.6-1.4)	1.0
Adam and Thorogood, 1981[45]	C/control	35 F MI	1.1 (0.6-1.8)*	
Slone et al., 1981[10]	C/control	206 NF MI	1.1 (0.9-1.4)	1.2
La Vecchia et al., 1987[48]	C/control	22 NF MI	1.9 (0.8-4.7)	1.8
Rosenberg et al., 1988[26]	C/control‡	NF MI		
		1-4 yr duration	1.2 (0.8-1.7)*	
		5-9 yr duration	1.2 (0.8-1.9)*	
		10+ yr duration	1.3 (0.7-2.4)*	
Stampfer et al., 1988[24]	Prospective	136 F + NF MI	0.8 (0.6-1.0)	0.9
Croft and Hannaford, 1989[25]	C/cohort	67 F + NF MI	1.0 (0.7-1.6)	1.3
Meta-analyses				
1. Without regard to adjustment for confounding 1.05 (0.94-1.17)				
2. Limited only to cohort studies[23-25] 0.85 (0.69-1.05)				
3. With adjustment for confounding 1.01 (0.91-1.13)				

RR, Relative risk; *CI,* confidence interval; *NF,* nonfatal; *F,* fatal; *MI,* myocardial infarction; *C/control,* case-control; *C/cohort,* case-cohort study (case-control study nested in a prospective cohort).

*Adjusted for age alone or crude data within a limited age range but unadjusted for confounders.

†Includes results from both studies without duplication.

‡There were 675 cases, but the number of exposed cases is not given.

and unadjusted results, yielded a relative risk of 1.05 (95% confidence interval, 0.94 to 1.17) (Table V). A meta-analysis limited to the three cohort studies,[23-25] in which bias may be expected to be minimized, revealed an estimate of 0.85 (95% confidence interval, 0.69 to 1.05). As previously noted, the meta-analysis of all 13 studies probably provides a slight overestimate of the true effect because only a few studies adjusted for confounding factors. In the five studies that did so, the estimate of effect was attenuated by a weighted average of 12%. We applied this estimated effect of uncontrolled confounding to the results of all studies that provided only age-adjusted relative risks according to the method suggested by Greenland.[34] The estimate from this meta-analysis, a relative risk of 1.01 (95% confidence interval, 0.91 to 1.13), probably provides the best guide to the true effect based on the published data. The estimated relative risk of 1.01 lies within the 95% confidence intervals of each of the age-adjusted estimates for the individual studies. The upper bound of 1.13 effectively excludes all but the most modest adverse effect.

Comment

The lack of trend with increased duration of past use, the apparent immediate decline in risk to baseline values after cessation of oral contraceptive use, and the lack of any duration effect in the excess risk associated with current use[11] point to a short-term mechanism rather than a more long-term effect, such as progression of atherosclerosis, to explain the increase in risk of myocardial infarction among current users. Ample biologic plausibility supports this conclusion. Oral contraceptives are known to have an adverse impact on coagulation, presumably through decreasing levels of antithrombin III and increasing levels of several clotting factors.[11, 37]

This conclusion is further reinforced by angiographic and anatomic studies of young women with myocardial infarction. Engel[38] found that oral contraceptive users appeared more likely to have a myocardial infarction without severe diffuse atherosclerosis than did nonusers. In a series of 76 angiograms among women 50 years of age or younger with a prior myocardial infarction, 27 of the 34 patients without serious coronary disease were current oral contraceptive users compared with 15 oral contraceptive users among 42 patients with coronary disease ($p < 0.001$). Of the 18 patients with myocardial infarction without any stenosis of 50% or more, 15 were oral contraceptive users ($p = 0.01$). Similar findings have been observed in smaller series of cases studied by angiography or at autopsy.[38, 39] In animal studies, monkeys eating a typical North American (atherogenic) diet who were given oral contraceptives had slightly less atherosclerosis than did those on the same diet that were given placebo.[40]

Data on the effect of past use of oral contraceptive on stroke risk are too sparse for a formal meta-analysis, and the findings have been inconsistent. The Collaborative Group Study of Stroke in Young Women[41] found a ninefold excess risk of thrombotic stroke and a twofold risk of hemorrhagic stroke in current users, but "there were no important differences between the

percentages of cases and controls who used oral contraceptives at any time," strongly suggesting no effect for past use; no actual data are provided. In contrast to those results and the findings from the Nurses' Health Study, the Walnut Creek Study[42] found a relative risk of 5.3 (95% confidence interval, 1.3 to 22.0) for subarachnoid hemorrhage in past oral contraceptive users, but there was only one case in the never use category (yielding a statistically unstable estimate), and five of the seven cases in past users were smokers and therefore at higher risk.[43] The Royal College of General Practitioners Study[12] found that past users had a relative risk of stroke of 3.6 (95% confidence interval, 1.5 to 8.5), and for subarachnoid hemorrhage specifically, 4.5 (95% confidence interval, 1.2 to 16.5) higher risks than they observed for current uesrs. More than two thirds of patients with subarachnoid hemorrhage smoked, so it is difficult to disentangle the effects of smoking and oral contraceptives. The Oxford Family Planning Study[44] also found a (nonsignificant) increase in risk of subarachnoid hemorrhage in past oral contraceptive users but with only three cases in the never use category.

The hormone dosages used in oral contaceptives has decreased markedly. Most of the oral contraceptive use among past users in the Nurses' Health Study and in other studies reviewed here took place when the dosages were relatively high compared with current practice. Although inconclusive, preliminary evidence suggest that the newer formulations carry a lower risk of myocardial infarction among current users than did the earlier preparations.[26, 35, 45-47] Thus it is likely that the newer preparations also will not carry a residual risk among past users. Collectively, the data from the Nurses' Health Study and the overview of the literature provide reassuring evidence that the risk of coronary heart disease among past users of oral contraceptives is approximately the same as for women who have never used them.

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Impairment of glucose tolerance: Mechanism of action and impact on the cardiovascular system

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Macrovascular diseases, especially coronary heart diseases, have been found to be linked to glucose intolerance. Insulin resistance in respect to glucose uptake in peripheral tissues seems to play an important role in the development of glucose intolerance, since subjects with coronary heart disease mainly are hyperinsulinemic. Insulin resistance may induce not only glucose intolerance but also hypertension, obesity, and dyslipoproteinemia (high very low–density lipoprotein and low high-density lipoprotein values), all variables that add to the risk of coronary heart disease. On the basis of these findings, a new syndrome has been postulated—syndrome X. This syndrome may be caused by inherited insulin resistance in skeletal muscles, and secondary to that arterial hypertension, obesity, and dyslipoproteinemia may develop. Insulin resistance in noninsulin-dependent diabetic persons and in hypertensive subjects is located in skeletal muscles, where insulin's ability to promote nonoxidative glucose metabolism is reduced. The key enzyme in this pathway, glycogen synthase, is proposed as the causal defect responsible for the insulin resistance state, at least in noninsulin-dependent diabetic patients. The pill (sex steroids) may induce a clinical situation that is similar to syndrome X. However, it is important to emphasize that many more studies are needed to substantiate these hypothetical mechanisms behind coronary heart disease. (Am J Obstet Gynecol 1990;163:292-5.)

Key words: Insulin resistance, glucose intolerance, coronary heart disease, sex steroids

Sex steroids (the pill) have been found to induce impaired glucose tolerance in a great many pill users.[1] Furthermore, an increased risk of hypertension, dyslipoproteinemia, increased body weight, and coronary heart disease has been reported.[1]

Therefore the question is, how may these events be linked together? Is there a common pathogenetic cause that may link these complications to the pill?

Recent investigations[2] have outlined that insulin resistance in respect to glucose disposal could be the underlying defect. Therefore the importance of insulin resistance in the development of glucose intolerance, arterial hypertension, dyslipoproteinemia, and coronary heart disease will be discussed in further detail in this short article. The cellular abnormalities responsible for peripheral insulin resistance will be considered.

Glucose intolerance

Glucose tolerance, as estimated by the oral glucose tolerance test, depends on several factors, but the most important are insulin secretion and insulin action. A close correlation has been found between these two variables in normal subjects, where they seem to compensate for each other. The result is that glucose tolerance is kept normal even if one of the variables is altered.[3] Thus in most subjects suffering from insulin resistance, it may be compensated by hypersecretion of insulin. Therefore these subjects will develop hyperinsulinemia both in the fasting state and after a meal. If β-cells are unable to produce enough insulin to overcome the insulin resistance, frank diabetes mellitus will result. Therefore insulin resistance may be present in a compensated form, for example, obesity, and an uncompensated form, such as noninsulin-dependent diabetes mellitus. In between normal glucose tolerance and frank diabetes (fasting hyperglycemia), a clinical state characterized by partial compensation of insulin resistance has been defined—impaired glucose tolerance—a clinical state with normal fasting plasma glucose values but postprandial hyperglycemia.

Glucose intolerance, both diabetes mellitus and impaired glucose tolerance, has been linked to macrovascular diseases, especially coronary heart disease.[4] Furthermore, glucose intolerance seems to be a common feature in subjects with arterial hypertension. In a recent article about 40% of hypertensive patients were glucose intolerant.[5] Also, dyslipoproteinemic subjects have been found to be more glucose intolerant than control subjects.[2] Thus taken together, glucose intolerance seems to be a common characteristic of subjects

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with dyslipoproteinemia, arterial hypertension, and obesity.

Because insulin resistance is the major underlying defect of glucose intolerance in the subjects described above, the following question may be raised: how does insulin resistance lead to hypertension, obesity, and dyslipoproteinemia?

Role of insulin resistance in the pathogenesis of arterial hypertension

In a recent population study of around 2500 subjects with arterial hypertension, about 40% suffered from glucose intolerance.[5] As many as 85% were either glucose intolerant or obese. Hyperinsulinemia was more frequent in hypertensive subjects than in normotensives, and hypertension was independently associated with hyperinsulinemia. (It means independent of body weight and glucose levels.) Insulin action was not measured in this study, but the high insulin levels indicate that hypertensive subjects were insulin resistant. In fact that conclusion has been supported by measuring peripheral insulin action by means of the euglycemic hyperinsulinemic clamp technique in lean subjects with arterial hypertension.[6] Thus the conclusion that insulin resistance may be of pathogenetic importance for the development of hypertension is based on solid ground, but more studies are needed for further clarification.

How can insulin resistance lead to arterial hypertension?

There are basically three explanations, which more or less are based on the fact that insulin resistance leads to hyperinsulinemia. In other words, compensation for insulin resistance may lead to hyperinsulinemia and hypertension.

Insulin has been found to play an important role in the regulation of sodium reabsorption in the distal tubules.[7] High insulin levels increase sodium reabsorption in a dose-dependent manner. Together with sodium, water is reabsorbed, and the result in an increase in exchangeable water as recently shown in diabetic patients with hypertension.[8] The mechanism for the development of hypertension seems especially to take place in glucose-intolerant subjects who have hyperinsulinemia. The mechanism may be an activation of sodium-potassium–adenosine triphosphatase activity in the distal tubules.[7]

It has also been claimed that hyperinsulinemia may increase the noradrenalin concentration in plasma and thereby the sympathetic tone. That mechanism could explain at least in part the arterial hypertension in insulin-resistant subjects.[8] However, only very high insulin concentrations (unphysiologic values) were able to increase noradrenalin concentrations and only about 50% compared with basal level. In that respect it is important to emphasize that noradrenalin values rises about 2.5-fold by upright posture. Therefore an increase in noradrenalin concentration as a result of hyperinsulinemia may play a minor role in the development of hypertension in insulin-resistant subjects.

The third explanation is based on the fact that intracellular sodium content has been shown to be increased in erythrocytes from hypertensive subjects.[5] This phenomenon may be explained by reduced activity of sodium-potassium–adenosine triphosphatase in the erythrocyte membrane secondary to cellular insulin resistance. If these abnormalities also take place in smooth muscle cells, it may result in narrowing of the lumen of small arteries and thereby explain the peripheral resistance demonstrated in hypertensive subjects. More studies are needed to prove this hypothesis.

Further evidence of the relationship between insulin resistance and arterial hypertension has been outlined recently when rats fed sucrose developed not only insulin resistance but also hypertension.[2] Thus in conclusion much evidence is in favor of the hypothesis that arterial hypertension–like glucose intolerance may be secondary to reduced insulin-mediated glucose uptake in peripheral tissues (muscles). Arterial hypertension may develop as a consequence of compensated insulin resistance but may also be from insulin resistance itself.

Role of insulin resistance in the development of obesity

Insulin resistance in respect to glucose disposal may develop because of environmental factors, such as hyperalimentation and reduced physical activity, but may also be of genetic origin.[10] In genetically obese rats, insulin resistance is located in muscle cells and not in fat cells.[11] This means that compensation for the reduced disposal of glucose in skeletal muscles by hyperinsulinemia may increase triglyceride synthesis in adipocytes and therefore lead to overweight. Hyperinsulinism may also stimulate the appetite and thereby add to the development of obesity. This mechanism for the development of obesity may take place in some subjects, whereas overeating may be the primary abnormality in others. In all obese persons, however, insulin resistance is an important clinical feature.

Role of insulin resistance in the development of dyslipoproteinemia

Subjects with abnormal glucose tolerance are characterized by high triglyceride values (very low–density lipoprotein) and low high-density lipoprotein cholesterol values.[2] Similar abnormalities has been described in subjects with hypertension.[2] Hypertriglyceridemia seems to be secondary to insulin resistance and hyper-

insulinemia. Highly significant correlations have been demonstrated between reduced insulin-mediated glucose disposal and very low–density lipoprotein values.[2] Furthermore, an increase in very low–density lipoprotein synthesis in the liver and a reduction in peripheral clearance of very low–density lipoprotein has been found in hyperinsulinemic insulin-resistant subjects.[2] Thus considerable evidence supports the hypothesis that hypertriglyceridemia is secondary to insulin resistance and hyperinsulinemia is present. Furthermore, reduced high-density lipoprotein cholesterol values seem to be linked to high very low–density lipoprotein values.

Role of insulin resistance in coronary heart disease

Resistance to insulin-mediated glucose disposal is associated very often with hyperinsulinemia, glucose intolerance, increased very low–density lipoprotein, and reduced high-density lipoprotein values and hypertension, all important variables for the development of arteriosclerosis and coronary heart disease.

That cluster of risk factors linked together has lead several researchers to propose a new syndrome, syndrome X, which is defined as follows: (1) resistance to insulin-mediated glucose disposal, (2) glucose intolerance, (3) hyperinsulinemia, (4) increased very low–density lipoprotein triglycerides, (5) decreased high-density lipoprotein cholesterol, (6) hypertension, and (7) increased fat mass. The inherited defect may be insulin resistance in skeletal muscles, whereas all other abnormalities may be secondary.

What is the cellular defect(s) responsible for insulin resistance in subjects with syndrome X?

Until now no studies dealing with that question have been carried out in subjects with well-defined syndrome X. Most investigations, however, have been carried out in glucose-intolerant subjects, that is, diabetic persons with or without the other characteristics of syndrome X. However, in vivo studies of insulin action in hypertensive subjects have also been published.[6] Hypertensive subjects suffer from insulin resistance only in peripheral tissues, whereas the liver seems to react adequately to insulin.[6] In obese subjects with noninsulin-dependent diabetes mellitus, liver, adipose tissue, and skeletal muscles are insulin resistant.[12] However, insulin resistance in skeletal muscles seems to play the quantitatively most important role and also seems to be primary to the defects in the other tissues.[12] Thus based on these facts, it seems meaningful to hypothesize that insulin resistance in skeletal muscles may be the primary defect and a genetic defect in subjects with syndrome X. However, further studies are needed to substantiate this hypothesis.

In skeletal muscles from both hypertensive subjects[6] and those with noninsulin-dependent diabetes mellitus,[12] the major defect in intracellular glucose processing is located in the nonoxidative pathway, that is, mainly glycogen synthesis. Because defects in this pathway also have been found in relatives of subjects with noninsulin-dependent diabetes mellitus, it may be the primary event in developing noninsulin-dependent diabetes mellitus (and syndrome X).

In obese subjects with noninsulin-dependent diabetes mellitus, the number of insulin receptors in skeletal muscle seems to be reduced. Furthermore, the ability of the insulin receptor kinase to stimulate external substrates is also reduced.[13] These two defects are common in obese persons with and without diabetes. Therefore the reduced receptor number and reduced kinase activity may not explain the difference in insulin action between the two groups. On the other hand, receptor abnormalities may at least in part explain the development of insulin resistance in obese subjects. Both defects may be of a secondary origin because they seem to be completely reversible by diet treatment.[14] The primary cellular defects responsible for the reduced insulin action in obese diabetic subjects must be located at the postreceptor level. One candidate could be the glucose transporter. Insulin-mediated glucose transport into muscle cells from obese persons with and without diabetes seems to be identical but reduced compared with lean control subjects.[15] However, reduced glucose transport activity may also be secondary because it can be induced by overfeeding and is completely reversible, at least in fat cells.[16] Furthermore, defects in insulin receptor number and kinase activity and in glucose transport activity cannot explain an isolated defect in the nonoxidative pathway. For that explanation, one needs specific defects in this pathway on the postreceptor and posttransporter level.

The key enzyme in glycogen synthesis is glycogen synthase. In lean subjects with normal glucose tolerance, that enzyme can be stimulated several fold by insulin, but in obese subjects the stimulation is significantly lower, and in obese diabetics, the enzyme activity is completely resistant to insulin.[17] That defect in glycogen synthase activity may explain the reduced glycogen synthesis in skeletal muscles from obese diabetic persons. Until now it has not been substantiated if it is the primary genetic defect.

In conclusion, insulin resistance in subjects with hypertension and noninsulin-dependent diabetes mellitus, and therefore supposedly also in subjects with syndrome X, seems mainly to be located in the nonoxidative pathway in skeletal muscles. Reduced glycogen synthase activity in skeletal muscles may be the primary defect in this syndrome. However, more studies are needed to emphasize that hypothesis.

Compensated insulin resistance may lead to syndrome X, whereas uncompensated insulin resistance in surplus leads to noninsulin-dependent diabetes mellitus.

Exogenous sex steroids, such as in the pill, may induce "syndrome X" by impairment of insulin action in skeletal muscles. However, the severity of this syndrome in pill users seem to be much less pronounced than in subjects with the genetic syndrome.

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Role of plasma lipoproteins in the pathogenesis of atherosclerotic disease, with special reference to sex hormone effects

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Plasma lipoproteins constitute a complex lipid transport system. Very low–density lipoproteins transport triglycerides to peripheral tissues, whereas low-density lipoproteins are the main carriers of cholesterol. Cholesterol transported in low-density lipoprotein enters body cells by way of the "low-density lipoprotein receptor pathway" but may also be taken up by macrophages by way of the "scavenger pathway." Excessive influx of cholesterol by way of the "scavenger pathway" may result in deposition of cholesterol in arterial walls and atheroma formation. In a yet incompletely known process of "reverse cholesterol transport," cholesterol is carried away from the tissues to the liver by high-density lipoproteins. The above-mentioned transport processes are regulated by a well-synchronized system that involves several enzymes and lipid transport proteins. Under normal conditions, the lipoprotein system is able to balance the flow of cholesterol and other lipids in both directions between the liver and peripheral tissues. This delicate balance may be disturbed by many factors, including contraceptive steroids. The metabolic steps influenced by administration of contraceptive steroids are summarized. (AM J OBSTET GYNECOL 1990; 163:296-304.)

Key words: Oral contraceptives, cholesterol, lipoproteins, lipoprotein lipase, hepatic lipase

Lipids by themselves are not soluble in plasma. They are transported in the form of soluble complexes with proteins known as lipoproteins. Plasma lipoproteins constitute a carrier system that provides the tissues with lipids for production and storage of energy and with cholesterol needed for cellular structures and for synthesis of steroid hormones. With regard to pathogenetic mechanisms of atherosclerosis, a major advance was achieved when the metabolic steps involved in cholesterol delivery to body cells, a sequence designated the low-density lipoprotein receptor pathway, was clarified in detail.[1] Although less is known about the removal of excess cholesterol and lipid from peripheral tissues, a well-synchronized system involving several enzymes and lipid transport proteins, as well as high-density lipoprotein, probably regulates a "reverse cholesterol transport."[2]

Under normal conditions, the lipoprotein system is able to balance the flow of cholesterol (and other lipids) in both directions between the liver and peripheral tissues. However, this delicate balance may be disturbed by several factors, such as diet, drugs, and hormones. Some of these disturbances are known to cause the formation of atherosclerotic lesions in the arterial wall. Accumulation of low-density lipoprotein in plasma is a well-established cause of atherosclerosis. Low plasma high-density lipoprotein, which possibly reflects an alteration in "reverse cholesterol transport," may be another contributing factor. The present review is limited to the above-mentioned pathways of endogenous cholesterol transport, with special reference to metabolic steps influenced by the administration of contraceptive agents. The pathways involved in exogenous (dietary) lipid transport have been recently reviewed elsewhere.[3]

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General outline of endogenous lipid transport

All lipoproteins share a common structure. Their surface layer consists of phospholipids and free cholesterol associated with protein components called apolipoproteins, whereas the lipophilic core region is filled with cholesteryl ester and triglycerides. In addition to chylomicrons that serve exogenous lipid transport, very low–density lipoprotein, low-density lipoprotein, and high-density lipoprotein can be separated from each other by sequential ultracentrifugation. High-density lipoprotein can be further separated into a light HDL_2 fraction and a denser HDL_3 fraction.

The liver provides triglycerides for peripheral tissues by secreting very low–density lipoprotein. The triglycerides are hydrolyzed and liberated from very low–density lipoprotein by the enzyme lipoprotein lipase,

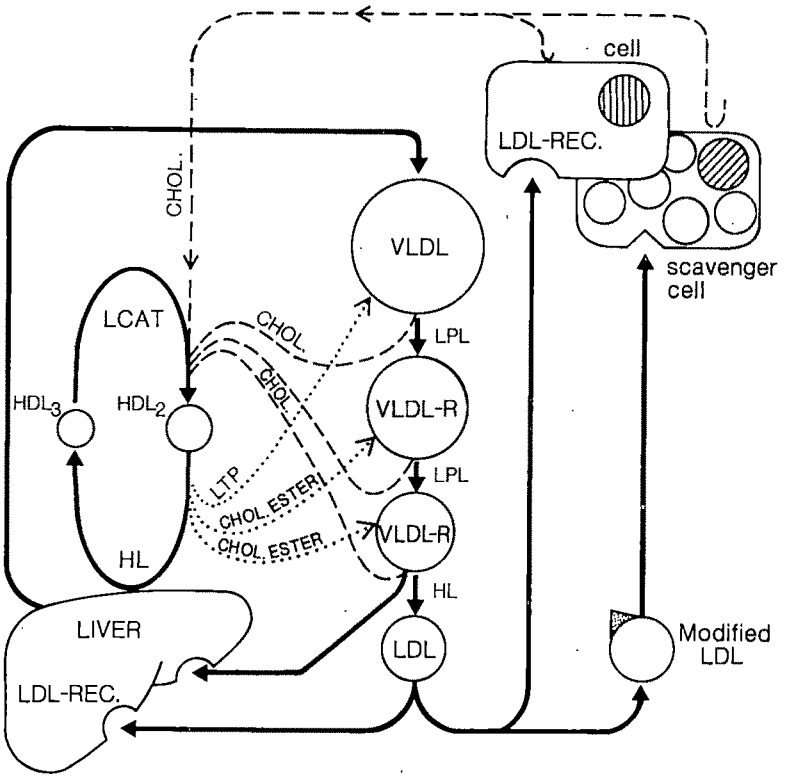


Fig. 1. Hypothetical scheme of cholesterol transport. *Dashed lines* indicate cholesterol flux from cells and lipolyzed very low-density lipoproteins *(VLDL)* and very low-density lipoprotein remnants *(VLDL-R)* to high-density lipoprotein 3 *(HDL_3)*, resulting in lecithin:cholesterol acyltransferase *(LCAT)*–catalyzed formation of HDL_2. *Dotted lines* indicate lipid transport protein *(LTP)*–mediated transfer of esterified cholesterol from HDL_2 to very low–density lipoprotein and VLDL-R, followed by conversion of HDL_2 into HDL_3 in a reaction catalyzed by hepatic lipase *(HL)*. *LPL*, Lipoprotein lipase; *LDL-REC*, low-density lipoprotein receptor.

which is attached to the endothelial cells in capillaries in extrahepatic tissues. The action of lipoprotein lipase promotes a gradual delipidation process in which smaller and denser remnants of very low–density lipoprotein (intermediate-density lipoproteins) are formed (Fig. 1). In addition to triglycerides, surface components (free cholesterol, phospholipids, and apolipoproteins except apolipoprotein B) are also removed from lipolyzed very low–density lipoprotein and transferred to high-density lipoprotein. Finally, small remnants of very low–density lipoprotein are converted into low-density lipoprotein, a step in which another enzyme, hepatic lipase, has a yet ill-defined role.

The function of low-density lipoprotein is to deliver cholesterol to body cells by way of the low-density lipoprotein receptor pathway. This pathway is initiated by the recognition and binding of the sole protein component in low-density lipoprotein, apolipoprotein B, to the low-density lipoprotein receptor. Body cells maintain their intracellular cholesterol homeostasis by up- or down-regulation of the number of low-density lipoprotein receptors on cell surfaces.[1,4]

High-density lipoprotein provides a mechanism for the removal of cholesterol from extrahepatic tissues to the liver. The free cholesterol derived from cells and from other lipoprotein classes is incorporated into the surface layer of HDL_3 particles where it becomes esterified in a reaction that is catalyzed by lecithin:cholesterol acyl transferase,[5] an enzyme activated by apolipoprotein A_1, the main apolipoprotein in high-density lipoprotein. The lecithin:cholesterol acyl transferase reaction contributes to the formation of larger, less-dense HDL_2 particles. The cholesteryl esters contained in HDL_2 are then transported to the liver by direct or indirect routes (Fig. 1).

Very low–density lipoprotein and triglyceride metabolism

Lipolysis of very low–density lipoprotein. In 1953 Nikkilä[6] observed that an intravenous heparin injection released a "clearing factor" into the circulation that caused a shift in lipids from β-globulins to α-globulins (from lower density lipoproteins to high-density lipoprotein) and resulted in a distribution of lipids "opposite to that found in many pathological states, that is, in atherosclerosis." This was an early description of the very low–density lipoprotein lipolytic process in

which clearing factor or lipoprotein lipase (releasable into the circulation by heparin) serves as a rate-limiting enzyme of very low–density lipoprotein catabolism. Hydrolysis of triglycerides by lipoprotein lipase results in shrinkage of the lipoprotein core, a situation in which the surface layer becomes too large and redundant. Its surplus constituents (free cholesterol, phospholipid, and apolipoproteins C and E) are pinched off the particles as discoidal structures,[7] which, on entering the plasma compartment, are rapidly converted into spherical high-density lipoprotein particles by the lecithin: cholesterol acyl transferase reaction. Alternatively, surplus material is taken up by preexisting HDL_3 particles, which result in formation of HDL_2 particles by lecithin: cholesterol acyl transferase. With the continuous loss of both core and surface lipids, very low–density lipoprotein remnant (intermediate-density lipoprotein) particles gradually diminish in size and ultimately give rise to low-density lipoprotein molecules (Fig. 1).

Although the precursor-product relationship between very low–density lipoprotein and low-density lipoprotein is beyond doubt, all very low–density lipoprotein does not generate low-density lipoprotein. Large triglyceride-rich very low–density lipoproteins are rapidly cleared from the circulation by the liver by way of a receptor-mediated process with relatively little conversion into low-density lipoprotein. Smaller very low–density lipoprotein particles containing less triglycerides and more cholesterol are more efficiently converted into low-density lipoproteins.[8, 9]

Several lines of evidence indicate that another lipolytic enzyme, hepatic lipase, located on the endothelial cells in liver sinusoids,[10] also participates in the very low–density lipoprotein–lipolytic process that converts very low–density lipoprotein remnants to low-density lipoprotein. This is suggested by studies that indicate accumulation of very low–density lipoprotein remnants during hepatic lipase inhibition in animals,[11-16] as well as in humans with inherited hepatic lipase deficiency.[17-19] A negative correlation was reported to exist between hepatic lipase activity and intermediate-density lipoprotein in patients with hyperlipidemia.[20] Large low-density lipoprotein enriched with triglycerides has been a common finding in patients with familial hepatic lipase deficiency,[17-19] possibly representing the final product of very low–density lipoprotein catabolism in these patients.[19]

Lipid transfer proteins and very low–density lipoprotein lipolysis. Plasma lipid transfer proteins promote a reciprocal exchange of triglycerides from very low–density lipoprotein with cholesteryl esters derived from high-density lipoprotein.[21, 22] The lipid transfer proteins also probably facilitate transfer of phospholipids from very low–density lipoprotein to high-density lipoprotein during lipolysis.[22] Lipolysis of triglyceride-rich lipoproteins is a major source of high-density lipoprotein phospholipids.[23] Enhanced activity of lipid transfer proteins has been demonstrated during in vitro lipolysis, probably because of preferred binding of lipid transfer proteins to lipolyzed (compared with nonlipolyzed) lipoproteins.[24] Similar mechanisms could operate in vivo, facilitating transfer of lipids from lipoproteins undergoing lipolysis to acceptor high-density lipoprotein.[22] Moreover, the lipid transfer proteins mediate a continuous core-lipid exchange, providing a constant flux of esterified cholesterol to the triglyceride-rich lipoproteins and triglycerides to high-density lipoprotein.

As delineated, in additon to supplying tissues with free fatty acids and partially hydrolyzed glycerides, very low–density lipoprotein catabolism generates low-density lipoprotein for cholesterol transport by way of the low-density lipoprotein receptor pathway. Moreover, very low–density lipoprotein catabolism gives rise to HDL_2 particles, which are involved in transporting cholesterol in the opposite direction. These pathways will be discussed.

Cholesterol transport

The low-density lipoprotein receptor pathway. Our understanding of the pathogenesis of hypercholesterolemia and its role in atherosclerosis development has been facilitated by the studies of Brown and Goldstein,[4, 25] who used familial hypercholesterolemia as a model. They convincingly demonstrated the crucial role of regulation of plasma low-density lipoprotein in body cholesterol transport. Low-density lipoprotein was shown to mediate the delivery of cholesterol to body cells by way of the low-density lipoprotein receptors possessed by almost all types of cells.[26] Initially, the low-density lipoprotein bound to the low-density lipoprotein receptor, was internalized together with the receptor, and was exposed to lysosomal enzymes that hydrolyzed the low-density lipoprotein particles, releasing free cholesterol in the cytoplasm. This incoming free cholesterol was found to exert the following three regulatory effects that served to maintain intracellular cholesterol homeostasis: (1) The released cholesterol suppressed the activity of the 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the rate-limiting enzyme of cholesterol synthesis; (2) the activity of acyl coenzyme A:cholesterol acyltransferase, which reesterifies excess cholesterol for storage as lipid droplets in the cytoplasm, was activated; and (3) the liberated cholesterol suppressed low-density lipoprotein receptor synthesis, preventing further influx of cholesterol.[1]

The low-density lipoprotein receptor concept ex-

plains how the cells are able to increase their uptake of cholesterol, if necessary, by increasing the synthesis of low-density lipoprotein receptors. Conversely, cells are able to down-regulate their LDL receptors when intracellular cholesterol concentration is increasing. The most common reason for down-regulation of low-density lipoprotein receptors in Western populations is a diet rich in cholesterol and saturated fat, which causes the hepatocytes to accumulate cholesterol. In an analogy to inherited low-density lipoprotein receptor deficiency (familial hypercholesterolemia), the reduced number of low-density lipoprotein receptors in the liver causes an elevated plasma concentration of low-density lipoprotein, which is detected as elevated plasma cholesterol. Because most of the circulating low-density lipoprotein is cleared by way of the liver, impairment of this route has important consequences. As will be discussed, low-density lipoprotein that has been denied the receptor-mediated pathway may undergo modification and be cleared by way of a low-density lipoprotein receptor-independent pathway, the "scavenger pathway."

The "scavenger pathway" and atheroma formation.

Turnover studies[27-30] indicated that in normal and receptor-deficient subjects, some of the low-density lipoprotein was removed from the circulation by way of a low-density lipoprotein receptor-independent pathway designated "the scavenger pathway." Monocyte-derived macrophages residing in arterial walls probably constitute an important part of the scavenger cell system.[25, 31] In addition to the low-density lipoprotein receptor, macrophages have receptors that recognize chemically modified low-density lipoprotein. Unlike the low-density lipoprotein receptor, the "scavenger receptor" is not down-regulated by increasing the cellular cholesterol content, thus allowing these cells to become engorged with esterified cholesterol.[32] During excessive influx of modified low-density lipoprotein, the cells assume the characteristic of "foam cells" filled with cytoplasmic lipid droplets. Several mechanisms operating in the arterial intima are able to modify low-density lipoprotein to promote its uptake by macrophages.[31] The cholesteryl esters stored in lipid droplets are continuously undergoing hydrolysis[33] and can probably be excreted from the cell if cholesterol acceptors (e.g., high-density lipoprotein) are available.

Development of the earliest atherosclerotic lesion, the fatty streak, is characterized by the accumulation of "foam cells" beneath the arterial endothelium. If the influx of low-density lipoprotein–derived cholesterol into the arterial wall is not balanced by an adequate cholesterol removal mechanism, the ability of scavenger cells to excrete the cholesterol is overwhelmed and atherosclerosis develops. These events have recently been comprehensively reviewed.[31]

High-density lipoprotein and reverse cholesterol transport

Origin of plasma high-density lipoprotein. Nascent high-density lipoprotein enters the plasma compartment as discoidal bilayer structures that contain mostly phospholipids, unesterified cholesterol, and apolipoprotein. Nascent high-density lipoprotein is secreted by the liver and intestine or is derived from lipolyzed very low–density lipoprotein (or chylomicrons).[34, 35] In the plasma compartment the bilayers are rapidly converted into spherical particles through the action of lecithin:cholesterol acyl transferase, which esterifies free cholesterol with fatty acid from the phospholipid lecithin. The cholesteryl ester molecules move between the layers and form a hydrophobic core, giving rise to small spherical particles in the HDL_3 density range.[7]

HDL subfractions. After maturation of nascent high-density lipoprotein to HDL_3 particles, these particles serve as acceptors for additional free cholesterol and phospholipids, both of which serve as substrate for the lecithin:cholesterol acyl transferase reaction. These constituents are derived from lipolyzed triglyceride-rich lipoproteins and from body cells. Uptake of cholesterol by high-density lipoprotein from peripheral cells may be by assimilation from cellular membranes or mediated by high-density lipoprotein receptors recognizing apolipoprotein A_1.[36] Such receptors are up-regulated by accumulation of intracellular cholesterol.[37, 38] With continuous flux of esterified cholesterol into the lipoprotein core, particle size increases and the average density shifts into the HDL_2 range. Although HDL_2 is formed by the combined effects of lipoprotein lipase and lecithin:cholesterol acyl transferase previously described, HDL_2 can be reconverted to HDL_3 by the combined effects of hepatic lipase and lipid transfer proteins (Fig. 1).

Alterations in plasma total high-density lipoprotein cholesterol concentration usually reflect alterations in HDL_2, which appears to be the subfraction sensitive to dietary, hormonal, and other perturbations. In contrast, HDL_3 cholesterol concentrations tend to remain stable or are much less modified. Major mechanisms involved in regulation of plasma high-density lipoprotein concentration will be discussed.

Rate of very low–density lipoprotein lipolysis in the regulation of high-density lipoprotein. Several studies have revealed a positive correlation between post-heparin plasma or adipose tissue activity of lipoprotein lipase and high-density lipoprotein cholesterol.[39-42] On this basis, it appears that the rate of very low–density

lipoprotein (and chylomicron) lipolysis is an important regulator of the plasma high-density lipoprotein level.[42, 43] This is supported by a variety of experiments in which lipoprotein lipase activity was stimulated (by administration of fat, alcohol, or insulin or by physical exercise) or suppressed (by diets low in fat or caloric intake and by insulin deficiency or insulin resistance) and in which changes in opposite directions occurred in high-density lipoprotein or HDL_2 but not in HDL_3.[44] Thus the high-density lipoprotein and HDL_2 concentrations may be low in patients with hypertriglyceridemia because of low lipoprotein lipase activity, which causes reduced flux of surface constituents that are used in HDL_2 formation. However, this does not explain why the high-density lipoprotein concentration may be low in patients with hypertriglyceridemia resulting from increased production of very low–density lipoprotein in the presence of normal lipoprotein lipase activity. To explain this, two other factors, lipid transfer protein activity and hepatic lipase ativity, must be considered.

Rate of cholesteryl ester transfer in the regulation of high-density lipoprotein. The lipid transfer protein mediates the transfer of cholesteryl ester from high-density lipoprotein to triglyceride-rich lipoproteins in exchange for triglycerides from these particles.[21, 22] Thus cholesteryl esters originating from the lecithin:cholesterol acyl transferase reaction in high-density lipoprotein are transported to very low–density lipoprotein and ultimately to low-density lipoprotein derived from very low–density lipoprotein catabolism. This provides a route of cholesterol transport from extrahepatic tissues to the liver. The rate of cholesteryl ester transfer from high-density lipoprotein is proportional to the amount of very low–density lipoprotein present at least during incubation in vitro.[45] If the same mechanism works in patients with hypertriglyceridemia, the result is formation of high-density lipoprotein that is deficient in cholesteryl ester and enriched in triglyceride. Since triglycerides provide a good substrate for hepatic lipase, the net result is a reduction in both core lipids, resulting in small, dense particles that resemble HDL_3. This could explain the occurrence of low high-density lipoprotein (HDL_2) cholesterol in subjects with hypertriglyceridemia with an increase in production of very low–density lipoprotein but normal lipoprotein lipase function.

Hepatic lipase in the regulation of high-density lipoprotein. The role for hepatic lipase in the degradation of high-density lipoprotein was suggested by studies showing an inverse relationship between hepatic lipase activity in postheparin plasma and the concentration of high-density lipoprotein or HDL_2.[46-50] Experimental studies suggested that HDL_2 was selectively degraded by hepatic lipase[51-54] and that inhibition of this enzyme in rats produced elevated levels of high-density lipoprotein.[55] Clinical studies[56, 57] have indicated that hepatic lipase is a sex steroid–sensitive enzyme suppressed by estrogen and stimulated by steroids with androgenic activity. Manipulations of postheparin plasma hepatic lipase activity by administration of a variety of sex steroids have shown that fluctuations in enzyme activity were, as a rule, accompanied by reciprocal changes in HDL_2 cholesterol levels.

It should be pointed out that removal of HDL_2 triglycerides (and probably phospholipids) by hepatic lipase is not sufficient to produce HDL_3 particles. Particles must also release large amounts of cholesteryl ester, which can be accomplished by the lipid transfer protein–mediated mechanism previously described. Together, these mechanisms contribute to reconverting HDL_2 into HDL_3 (Fig. 1). In addition, experimental studies have suggested that esterified cholesterol may be released directly from high-density lipoprotein particles to hepatocytes, or receptor-mediated uptake of high-density lipoprotein particles into the liver may occur.[58]

In hypertriglyceridemia, enhanced core-lipid exchange produces triglyceride-rich high-density lipoprotein that is efficiently hydrolyzed by hepatic lipase. This accounts for the common finding of a reduced high-density lipoprotein cholesterol level, with predominantly small particles in the HDL_3 density range.

Lecithin:cholesterol acyl transferase activity in the regulation of high-density lipoprotein. Lecithin:cholesterol acyl transferase catalyzes the esterification of free cholesterol on the surface of lipoproteins the preferred site being the surface of high-density lipoprotein, particularly the more dense particles in the HDL_3 subfraction.[59] Subsequently, the cholesteryl esters are incorporated into the lipophilic core of high-density lipoprotein, creating a concentration gradient for acquisition of more free cholesterol arriving from body cells and other lipoprotein fractions. Further action by lecithin:cholesterol acyl transferase, along with acquisition of other constituents from the very low–density lipoprotein lipolytic pathway, results in the development of larger and less dense HDL_2 particles (Fig. 1).

Mechanisms of "reverse cholesterol transport." Unesterified cholesterol is continuously moving from cells and lipoprotein surfaces to the surface of high-density lipoprotein. This cholesterol efflux is maintained by a concentration gradient that is generated when lecithin:cholesterol acyl transferase–derived cholesteryl esters are displaced from the high-density lipoprotein surface into the core and subsequently removed from high-density lipoprotein by lipid transfer protein activity. Alternatively, high-density lipoprotein particles may bind to high-density lipoprotein receptors while incorporating cellular cholesterol.[36] Receptors in-

volved in this process recognize apolipoprotein A_1 and are up-regulated when intracellular cholesterol concentration increases.[37] Cell culture studies have suggested that such high-density lipoprotein receptor-mediated removal of unesterified cholesterol occurs from macrophages that have accumulated modified low-density lipoprotein.[38]

Esterification of cholesterol by lecithin:cholesterol acyl transferase followed by a constant redistribution by lipid transfer proteins of cholesteryl esters to the very low–density lipoprotein −>low-density lipoprotein pathway maintains a continuous flow of cholesterol moving from the periphery to the low-density lipoprotein receptor pathway. Cholesteryl esters may arrive in the liver as components of very low–density lipoprotein remnants that are taken up by low-density lipoprotein receptors, or they may be retained in particles converted to low-density lipoprotein, also to be taken up by low-density lipoprotein receptors, thus ultimately completing a cycle of "reverse cholesterol transport."

Other mechanisms may also be important in "reverse cholesterol transport." Apolipoprotein E–containing high-density lipoprotein (a subfraction in the HDL_2 density range) binds hepatic low-density lipoprotein receptors and E receptors and therefore may be taken up by the liver.[60] Also, other types of receptor-mediated uptake have been suggested.[58] Experimental studies have demonstrated that pretreatment of high-density lipoprotein particles with hepatic lipase stimulates uptake of cholesterol from high-density lipoprotein to hepatoma cells.[61, 62] However, transfer was limited mainly to unesterified cholesterol[62] and did not indicate significant cholesteryl ester flux.

Low-density lipoprotein, high-density lipoprotein, and the development of atherosclerosis

During accumulation of low-density lipoprotein in plasma caused by overproduction or insufficient clearance by the low-density lipoprotein receptor pathway, large numbers of low-density lipoprotein molecules find their way through the endothelial lining of arterial walls. As previously described, low-density lipoprotein may undergo modification, which enables macrophages and smooth muscle cell to internalize them. Accumulation of lipid-laden "foam cells" and the inability of "reverse cholesterol transport" mechanisms to remobilize the cholesteryl esters probably initiate the atherosclerotic process.

Although there is no doubt about the atherogenicity of elevated plasma low-density lipoprotein cholesterol levels, the role of plasma high-density lipoprotein cholesterol concentration as an indicator of "reverse cholesterol transport" efficacy remains unresolved. It is usually thought that high high-density lipoprotein concentration indicates high cholesterol removal capacity from peripheral tissues, including arterial walls. Indeed, an abundant presence of high-density lipoprotein acceptor molecules for receptor-mediated or receptor-independent removal of cholesterol from lipid-filled macrophages and smooth muscle cells would obviously promote the initial step of "reverse cholesterol transport," and be in line with epidemiologic evidence indicating that elevated high-density lipoprotein cholesterol protects against atherosclerosis.[63]

On the other hand, a *low* high-density lipoprotein cholesterol level associated with increased atherosclerosis risk may also, in some situations (e.g., in hypertriglyceridemia), reflect increased "reverse cholesterol transport." This indicates that an enhanced rate of "reverse cholesterol transport" cannot be unequivocally regarded as an antiatherogenic phenomenon. In fact it has been suggested that efficient transfer of esterified cholesterol to potentially atherogenic lipoproteins (very low–density lipoprotein and low-density lipoprotein) could promote atherosclerosis.[22]

Metabolic steps influenced by the administration of contraceptive steroids

Very low–density lipoprotein and triglyceride metabolism. Most previous studies indicate the following: (1) that contraceptive estrogens elevate plasma very low–density lipoprotein and triglyceride levels, (2) that androgenic progestins derived from 19-nortestosterone reduce plasma very low–density lipoprotein and triglyceride levels, whereas progesterone-derived progestins have little effect, and (3) that in combination preparations, the relative potencies of estrogen and progestin determine the net effect on plasma very low–density lipoprotein and triglyceride levels.[56] The plasma triglyceride-elevating effect increases with estrogen dose[64-66] and is opposed more effectively by androgenic progestins (e.g., levonorgestrel) than by nonandrogenic progestins (e.g., desogestrel).[67, 68]

The plasma triglyceride-elevating effect of estrogens is the result of increased production of very low–density lipoprotein,[69-71] whereas no reduction in very low–density lipoprotein clearance has been reported.[69-72] Purely androgenic steroids are known to stimulate removal of plasma triglycerides,[73, 74] and there is some evidence for a similar effect produced by estrogen-progestin combinations.[70, 71] Plasma triglyceride effects are not mediated by changes in lipoprotein lipase activity.[56] It is not clear whether up- and down-regulation of hepatic lipase activity by estrogen and progestin contributes significantly to alterations in plasma very low–density lipoprotein and triglyceride levels during oral contraception.

Metabolism of low-density lipoprotein. In estrogen deficiency (postmenopausal women, men) marked

suppression of plasma low-density lipoprotein cholesterol usually occurs during the administration of estrogen.[56, 75] This has been attributed to estrogen-induced stimulation of low-density lipoprotein receptor activity demonstrated in animal[76, 77] and cell culture[78] experiments. However, premenopausal women respond differently, with no reduction in low-density lipoprotein cholesterol during contraceptive estrogen administration.[69]

Most of the earlier combination oral contraceptives tended to increase plasma concentration of low-density lipoprotein cholesterol.[79] The elevation was smaller with "estrogen-dominant" preparations than with "progestin-dominant" preparations[79] and greatest with preparations containing androgenic progestin.[80] The mechanisms behind the low-density lipoprotein–elevating effect of androgenic progestins[68] has not been clarified. Theoretically, stimulation of hepatic lipase activity by androgenic steroids could facilitate conversion of very low–density lipoprotein remnants to low-density lipoprotein. In association with estrogen-induced stimulation of very low–density lipoprotein production, this could result in low-density lipoprotein elevation. Alternatively, progestins might act as antiestrogens down-regulating low-density lipoprotein receptor activity. Neither of these possibilities has been explored adequately.

The content of triglycerides in low-density lipoprotein is increased with most oral contraceptive preparations.[64] This triglyceride-enriched low-density lipoprotein differs from the large buoyant low-density lipoprotein reported in hepatic lipase deficiency states[19] by manifesting a decreased flotation rate.[81, 82] Such a compositional change could result from increased lipid transfer protein–mediated exchange of cholesteryl ester and triglyceride between very low–density lipoprotein and low-density lipoprotein. This would probaby occur if the amount of circulating triglyceride-rich lipoproteins is increased during oral contraceptive administration.

Metabolism of high-density lipoprotein. Alterations in plasma total high-density lipoprotein cholesterol concentration during the administration of different oral contraceptives are caused mainly by alterations in the steroid-sensitive subfraction HDL_2.[49, 56, 83] Estrogens cause an elevation of HDL_2, whereas progestins with androgenic activity have the opposite effect. The relative potencies of estrogen and androgen determine the net result.[56] Estrogens act by at least two mechanisms: suppression of hepatic lipase activity, causing reduced conversion of HDL_2 into HDL_3, and increased synthesis of apolipoprotein A_1.[69] Androgenic progestins stimulate hepatic lipase activity,[83] and androgens suppress synthesis of apolipoprotein A_1,[84] which explains why estrogen-induced high-density lipoprotein elevations may be opposed or overwhelmed by the progestin component in oral contraceptives. Elevation of plasma very low–density lipoprotein produced by many oral contraceptives promotes lipid transfer protein–mediated removal of cholesteryl ester from high-density lipoprotein, which also contributes to decreased plasma high-density lipoprotein cholesterol. As previously discussed, it is unclear whether effective "reverse cholesterol transport" is antiatherogenic. Even if it were, its effectiveness could not be judged on the basis of plasma high-density lipoprotein cholesterol concentration. Thus the clinical significance of high-density lipoprotein cholesterol fluctuations induced by oral contraceptives remains uncertain.

The great majority of reported studies concerns earlier generations of oral contraceptives. Therefore some of the results may be irrelevant with regard to newer low-estrogen, low-progestin preparations, which have little effect on plasma low-density lipoprotein or high-density lipoprotein cholesterol.[85]

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Disorders of the hemostatic system and the risk of the development of thrombotic and cardiovascular diseases: Limitations of laboratory diagnosis

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The relationship between hemostatic abnormalities and thrombotic and cardiovascular diseases is summarized. All known congenital and acquired abnormalities in the biochemistry of hemostasis are related to thrombotic and cardiovascular diseases in the way that would be expected on the basis of theories about the role of balances between coagulation and fibrinolysis and between activating and inhibiting factors. Notwithstanding the consistency between theory and observed abnormalities, a causal relationship between biochemical abnormality and clinical symptoms has been proved only in a limited number of situations, and it is possible that certain abnormalities only (or also) mark pathologic events. The limitations of laboratory diagnosis of hemostatic disorders in relation to hemostasis as a local process are discussed. It is proposed that more attention be paid to methods of evaluating the local aspects, for example, methods that assess reaction products in the circulation and that can provide an averaged message of the local phenomena. In addition, such methods can provide information about the dynamic balances in the hemostatic system, whereas historically more attention has been paid to the static balances in the potential of hemostatic processes. (AM J OBSTET GYNECOL 1990;163:305-12.)

Key words: Fibrinolysis, coagulation, cardiovascular diseases, hemostatic disorders

The reaction to damage or trauma can result in the formation of platelet or fibrin deposits for temporary function in hemostatic plugging and support of cell growth in subsequent tissue repair. The formation and dissolution of the deposits are usually carefully regulated, and ideally the occurrence is confined to the exact time when the deposits are needed. Abnormalities in either direction of defective or excessive deposit formation are known. In addition to abnormalities in tissue repair (e.g., organized thrombi, deformations in persons with hemophilia,[1] excessive scar formations, and induced damage, such as valve destruction), overt symptoms such as either thrombosis or bleeding can occur.

The process of platelet or fibrin formation can be triggered by tissue damage and trauma. Moreover, next to clearcut macro damages, such as bruises and cuts, it has been proposed that micro damages occur continuously in the body.[2] Such micro damages might be at the level of single cells. It is suggested that they occur frequently in normal life and result in an almost continuous low-grade action of the coagulation system. To counteract this low-grade coagulation action, the fibrinolytic system should similarly exert an almost continuous low-grade action. The work of Astrups[2] implies that in regard to their potential, the fibrin-forming and removing systems should be in balance, as well as in their low-grade action. In other words, we can distinguish two balances: the static balance in potential and the dynamic balance in action.[3]

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Hemostatic disorders and clinical implications

Congenital disorders. Several hereditary hemostatic disorders have been identified that usually affect the performance of a single factor and cause either bleeding or venous thrombosis. In recent years it has become apparent in the Netherlands that the occurrence of hereditary thrombophilia has a higher provisionally estimated prevalence (1:3000) than the much earlier and better known hemophilia (1:15,000).[4,5]

We can group these hereditary hemostatic disorders into categories on the basis of known mechanisms. As shown in Fig. 1, *A*, a balance between coagulation and fibrinolysis puts these two processes in opposite situations. Defective coagulation results in bleeding, but defective fibrinolysis results in thrombosis, whereas bleeding can be induced by excessive fibrinolysis or defective coagulation. For all aspects, multiple examples of hereditary single-factor deficiencies are available (Tables I and II).

A balanced approach can be extended as shown in Fig. 1, *B*, to a balance within each system. Both the coagulation and fibrinolytic systems are cascade types of processes, in which activation is achieved by appro-

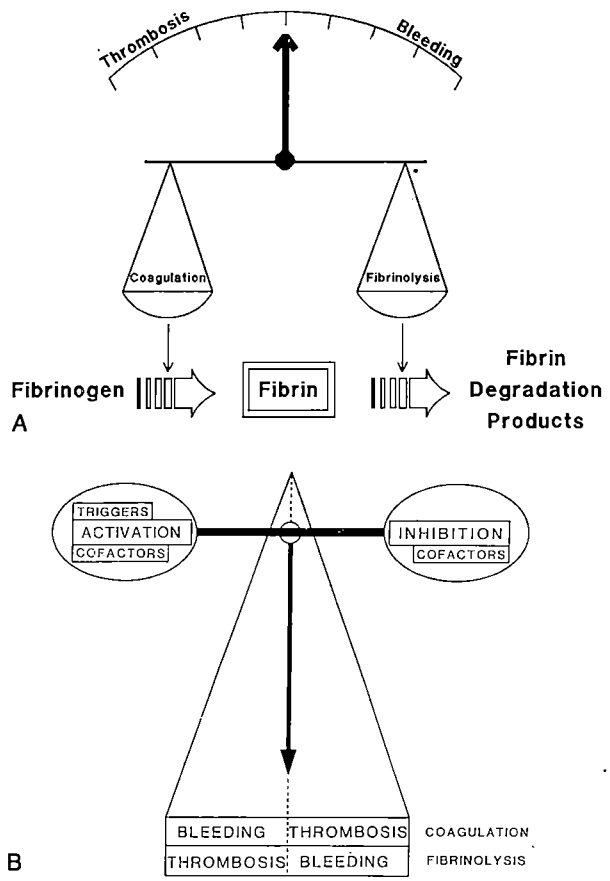


Fig. 1, A-B. Balances between the systems of coagulation and fibrinolysis and between activating and inhibiting components of these systems in relation to clinical symptoms of thrombosis and bleeding in case of imbalance.

priate limited proteolysis or conformational changes and in which damping is achieved by inactivation. Both opposing actions (activation and inhibition) can have cofactors for action, and activation requires triggering. In Fig. 1, *B*, the balance within the system is expressed in a cartoon, which shows both the opposite actions of activity promoting factors and inhibitory factors and the opposite positions of coagulation and fibrinolysis.

In Tables I and II known single-factor deficiencies in coagulation (except platelets) and fibrinolysis are divided into two clinical categories: bleeding and thrombosis. Fibrinogen is discussed separately (see below). For the threshold levels shown in Tables I and II, above or below which clinical effects become relevant, the choice of one clinician/author is cited where possible.[6]

The data in Tables I and II mainly concern venous thrombosis, since knowledge of arterial thrombosis in relation to single-factor deficiencies is scanty.[7-10] For dysfibrinogenemia, a clearcut relationship exists between arterial thrombosis and single-factor abnormality,[10] whereby expression of both arterial and venous thromboembolic complications can occur in one family or patient. Recently in young adults with arterial occlusive disease, protein S deficiency has also been found (8%), but no protein C or clear antithrombin III deficiency.[7] Evidence of a protective effect has been given for single-factor deficiencies in factor VIII or von Willebrand factor.[11] Conversely, elevations in the levels of these factors have been observed regularly, such as in 24% of patients with early (before 45 years) onset of arterial occlusive disease.[7]

Knowledge about the relationship between single-factor deficiencies and venous thrombosis has been obtained largely by the study of familial venous thrombosis. Similar studies on familial arterial thromboembolic complications are also needed for this aspect of arterial thrombosis. So far the selection of patients for venous thrombosis has not resulted in a large overlap with arterial thrombotic complications. In a study on venous thrombosis performed in the Netherlands, only 3% of patients had both arterial and venous thromboembolic problems, most of which were related to dysfibrinogenemia.[4] It should be evaluated whether this finding indicates that venous and arterial diseases are related to different biochemical deficiencies in hemostasis (option 1). It is also possible that deficiencies in biochemical hemostasis are equally important for both venous and arterial symptoms but that other factors determine whether the expression is venous or arterial (option 2). The identification of such a putative essential difference in the pathogenesis of hemostatic disorders would be an important goal of future research. In the near future, further knowledge about familial arterial disease will be needed. The families of young adults with arterial occlusive disease and protein S deficiency[7] should be studied to explore whether option 2 occurs for protein S.

Risk markers. For arterial disease, alterations in several variables of hemostasis have prognostic value. These alterations are indicated in Tables I and II as "prognostic significance" (PS). The major hemostatic deviations associated with arterial diseases are increased fibrinogen, increased factor VIIc, and increased activity of plasminogen activator inhibitor-1 (PAI-1)/decreased tissue-type plasminogen activator (t-PA) activity.[12-23] Theoretically these alterations can cause increased coagulation or reduced fibrinolysis in keeping with pathogenetic theories. However, it is possible that the alterations are not causal to the clinical expression but merely reflect an underlying mechanism or are consequences of other alterations and function as markers.

In the balance between coagulation and fibrinolysis, fibrinogen plays a central role, with the possibility that abnormalities change the balance in both directions of clinical symptoms (Fig. 1, *A*). Patients with congenitally abnormal fibrinogens (dysfibrinogenemia) can either

Table I. Deviations in the coagulation system in relation to symptoms

Coagulation					
Bleeding	*Thrombosis*		*Bleeding*	*Thrombosis*	
	Activation			Inhibition	
<40%	II			AT III	<75%
<10%	V			Protein S	<65%
<15%	VII	↑ PS		Protein C	0 or < 65%†
<25%	VIII	*			
<50%	vWF	*		HepCoF II	
<25%	IX			—	
<30%	X				
<50%	XI				
‡	XII	<50%‡			
	PK				
	KNG				
	—				

The indicated values are percentages of normal and are threshold levels for clinical expression (see text). When no mark or level is indicated for a factor in one of the categories, a deviation assocated with hemostatic disorders is not present or knowledge is absent or controversial at present.

vWF, von Willebrand factor; *PK,* prekallikrein; *KNG,* kininogen; *AT III,* antithrombin III; *PS,* prognostic significance.

*Elevated levels are frequently found in groups with venous[4] and arterial thromboembolic diseases,[7, 64] and reduced levels appear protective.[11]

†Protein C deficiency is clinically dominant in about 5% of heterozygous cases[4, 65] and clinically recessive for other heterozygotes.[66]

‡Bleeding in homozygous factor XII deficiencies is rare.[67] In families with members with around 40% factor XII, a thrombotic diathesis has been observed.[68] (See text and other sources.[12, 64, 69, 70])

Table II. Deviations in the fibrinolytic system in relation to symptoms

Fibrinolysis					
Bleeding	*Thrombosis*		*Bleeding*	*Thrombosis*	
	Activation			Inhibition	
	plasminogen	<65%	<80%	α_2-AP	
*	t-PA	↓ PS†	<5%	XIII	
	u-PA		‡	PAI-1	↑ PS
	—			HRG	>145%
				PAI-2	
				—	

The indicated values are percentages of normal and are threshold levels for clinical expression (see text).

When, for a factor, no level or prognostic significance is indicated in one of the categories, deviation associated with hemostatic disorders is not present or knowledge is absent or controversial at present.

*Anecdotal reports indicate that elevated t-PA activity[71, 72] relates to a bleeding diathesis.

†Ten percent to 12% of patients with venous thrombophilia have an abnormally low response in the venous occlusion test,[73, 74] which an abnormality relates to a poor prognosis for recurrences,[74] and this abnormality shows familial clustering,[75] or according to preliminary data, may have a genetic cause.[76]

‡Two situations with abnormally low PAI-1 and a bleeding diathesis have been reported.[77, 78] (See text and other sources.[22, 23, 79-81])

have no symptoms (the majority of known cases), a tendency to bleed (one third of cases), or a tendency to develop thrombosis (20%), depending on the abnormality in the fibrinogen molecule.[10] Consistent with the theories, the tendency to develop thrombosis has been explained in two cases by an abnormality in the function of fibrinogen in the regulation of fibrinolysis.[24, 25]

High plasma fibrinogen levels are recognized further in most studies as an important risk marker for ischemic heart disease[12-16] and nonhemorrhagic stroke.[13, 20] Increased fibrinogen levels have also been observed in asymptomatic peripheral arterial disease[18] and in patients after myocardial infarction,[26] especially in those with recurrencies.[17] They correlate with the angiographic score in one study[19] but not in another.[27] In addition to the demonstration of fibrinogen as a risk marker, it is also believed to have a causal role in cardiovascular disease. This is related to the effects of high fibrinogen levels on viscosity,[28] platelet aggregation,[29] and thrombus size.[30] High fibrinogen levels also affect the amount of fibrinogen in the vessel wall, which results in an increase in the accumulation of fibrin when coagulation occurs.[31, 32] The amount of fibrin in lesions is indeed increased[33] and can act as a diffusion block.[34] It can contribute to atherosclerosis by cuffing of vessels,

resembling perivascular manipulation, which produces a very rapid development of atherosclerosis in animals.[35] The establishment of high fibrinogen levels as a risk factor rather than as a marker still requires that interventions in the levels have an effect.

Possible double function of risk markers. For the relationship between abnormalities in the variables of hemostasis and clinical symptoms (Tables I and II), all the alterations in the biochemistry of hemostasis are theoretically consistent with the clinical symptoms. Nevertheless, this consistency does not necessarily imply that all alterations are causally related to the clinical symptoms. However, causal relationship is not excluded but in most circumstances is not proved. According to the criteria for establishing a relationship between congenital defect and venous thrombophilia,[5] sufficient evidence has been provided only for antithrombin III and proteins C and S deficiency.[5] In other cases evidence is still being gathered. In various situations the alterations may only be markers of an underlying mechanism.

The presence of such remarkable consistency between abnormality and expected symptoms presents the third alternative that markers are contributing to aggravation of the symptoms at the same time. In this latter combination, a strict distinction between causal factors and markers is no longer relevant.

It has recently been proposed to group a particular set of alterations together into what has been called "syndrome X."[36] In this syndrome, a link has been proposed between insulin resistance (as an underlying common pathway) and central obesity, hypertension, increased triglycerides, and decreased high-density lipoprotein. Elevations in PAI-1 can also be added to this syndrome. As shown by Juhan-Vague et al.,[37, 38] there is a clear correlation between insulin, triglycerides, and PAI-1. Insulin has been shown to increase PAI-1 production by hepatocytes.[39, 40] We can also add to this, further mechanistic links with hemostasis. Thus insulin increases the synthesis in cultured hepatocytes of fibrinogen after prolonged exposure.[41] In addition, a link between triglycerides (mainly the composition and presence of factor XII triggering fatty acids such as stearates) and factors XII and VII activation has been suggested.[42, 43] It can be suggested that the three major alterations in hemostatic aspects (factor VII, fibrinogen, and PAI-1), prognostic for cardiovascular diseases, may theoretically be added to syndrome X to create syndrome X+.

These mechanistic links between all alterations related to cardiovascular diseases are too striking to ignore, but apparently the statistical evaluation of the individual factors shows them in many cases to be also independently related to cardiovascular diseases. It may be pertinent to change the scope here and try to identify combination formulas and replace the desire to identify independent risk factors for the desire to understand why mechanistically linked alterations can show statistically independent risks. A possibility for the latter resides in the above-raised possibility that factors can show a combination of being a marker and an aggravating factor and that the degree of reaction to a metabolic change is genetically independently regulated or subject to major polymorphisms.

Individuals at risk. Changes in plasma levels, such as those that can be induced by oral contraceptives, should not be judged according to magnitude only. In addition to large changes, smaller changes are also of importance for persons with a plasma level that is already at the edge of the normal distribution. Even a relatively small change can bring such individuals outside the normal range and will specifically involve components that apparently need a tight regulation of plasma levels. Similarly, even small changes (in the "wrong" direction) in heterozygotes for a deficiency, such as antithrombin III deficiency, can be deleterious for those individuals. In most persons with normal plasma levels, such a small change is generally of no consequence. Thus such quantitatively small changes may be relevant only for a small percentage of the population but nevertheless should be considered. In this respect factors with a strict regulation of plasma levels may be relevant (e.g., antithrombin III).

Another individual risk lies in individually variable combinations of multiple changes. This can be illustrated for oral contraceptive use. Although in oral contraceptive–taking groups as a whole, both "procoagulant" and "profibrinolytic" changes occur and may seem compensatory, in some persons no such compensation was seen.[44] Therefore the use of oral contraceptives may produce individual profiles that are different from the average trend and may either be combined to a shift toward increased risk of thrombosis or toward bleeding complications.[44]

Taking these individual aspects into account, it appears that in theory any change in hemostatic variables, induced by a drug, will place some persons at risk for clinically relevant alterations in hemostasis. It will be important to identify those persons and exclude them or alternatively to develop drugs that induce minimal or no changes in hemostatic variables.

Interestingly, the termination of a drug or even modification of a life-style with an impact on hemostatic variables can give similar effects.

Limitations of laboratory diagnosis of hemostasis

It is most certainly utopic to assume that in the future, all thrombotic and cardiovascular diseases will be predictable or explainable by laboratory diagnosis of hemostasis. In most cases multiple factors contribute in a

complex way, which include individual differences. The present possibility to explain 31% of clearcut familial thrombophilia only by measurable defects in hemostasis (using most available hemostasis assays in 1988[4]) is rather meager. The present predictive power of risk factors is also rather low. We can blame our limited knowledge of hemostasis for that, but it can also be proposed that our limitation in diagnosing the mainly local processes of hemostasis in samples of circulating blood is a crucial factor (Fig. 2). This aspect will be elaborated on and an improvement for the near future will be discussed next.

Local aspects versus systemic measurement. The potential of the hemostatic system is determined by local concentrations of activating, inhibiting, and regulating components that at a particular place become involved in coagulation, platelet action, and fibrinolysis. We can determine the concentration of circulating factors in blood but cannot determine the local situation that involves accumulation of some components on receptors or structures formed during the process, such as fibrin and activated platelet masses, and that involves local cellular reactions of endothelium and platelets.

In recent years it has become clear that local aspects of the hemostatic processes are much more significant than previously thought. The platelet contribution to local coagulation was already well appreciated and includes various more interactions.[45,46] Also notable is the release of large amounts of PAI-1, which can be modulated by the potency of coagulation.[47] The involvement of endothelium has especially become more clear. The following two examples of endothelial involvement in both coagulation and fibrinolysis will illustrate this point.

Endothelium and coagulation and fibrinolysis. The quiescent endothelium contributes to the anticoagulation process by providing the receptor thrombomodulin, which is essential in damping the coagulation cascade by way of protein C. Endothelium further synthesizes the cofactor for protein C action, protein S, and provides a binding site for this protein. Nawroth and Stern[48] have postulated that the endothelium can change its contribution in hemostasis from anticoagulant, which is the condition of the quiescent cell, into procoagulant when the cell becomes perturbed. The perturbed cells start to express tissue factor, and a complete surface-bound process of coagulation with binding sites for factors IXa, VIIIa, X, and Xa is facilitated, which results in the local generation of thrombin. Evidence is provided that this change involves a set of coordinated changes (more than mentioned above), all of which contribute to a shift from anticoagulation to procoagulation.

It is difficult to diagnose the endothelial condition because most components are endothelium bound. One possible circulating marker of the perturbed condition of the endothelial cell that deserves mention is PAI-1, which is made in larger quantities by perturbed cells. PAI-1 is one of the few released factors in this process. It is possible that part of the observed importance of PAI-1, as a prognostic indicator for postoperative thrombosis[49] and recurrent myocardial infarction[22] and its elevation in coronary artery disease,[50-52] signals the presence of perturbed endothelial cells somewhere in the vascular tree.

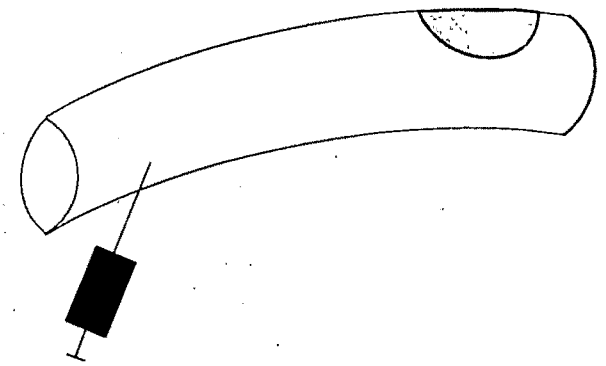


Fig. 2. Cartoon depicting our present practice of analyzing a distantly collected blood sample, whereas hemostatic processes are usually local. Only a limited answer can be expected regarding whether the potential of the system will be adequate in the local process and whether the process at the locus develops appropriately for healing.

An important contribution of endothelium to fibrinolysis is the acute release of t-PA in response to triggers, notably those derived from coagulation and platelet activation. The significance of this acute release is to provide t-PA locally in high concentrations at the right moment. As shown by several studies,[53-55] the presence of t-PA before clot formation results in a much more efficient lysis than does t-PA that is available after the formation of the clot. The timing of the availability of t-PA, relative to fibrin formation, determines the impact of the acutely released t-PA.

The phenomenon of acute release of t-PA suffers from tachyphylaxis.[56, 57] This applies only when the same trigger of the release is repeatedly involved. When other triggers of the acute release are used as a second or subsequent trigger, no tachyphylaxis occurs,[56] which indicates that repeated or chronic stimulation of the endothelium can result temporarily in periods of poor reactivity. At present the capacity of the vessel wall to release t-PA is tested frequently by infusion of desmopressin acetate.[58] This is a systemic test providing data on generalized or large abnormalities.

Future perspectives in laboratory diagnosis of hemostasis. In laboratory diagnosis we must distinguish

between two approaches. The first approach is the study of the potential of the systems by assessment of supply of factors and the functioning of the system by in vivo and in vitro tests. The second approach is the study of the action of the systems as reflected in its reaction products. In particular the assessment of the action of the systems can provide progress in the near future.

The action of the system is marked by the occurrence of several reactions involving release of components from cells, changes in membranes, limited proteolysis, change in functions of proteins, and complex formation. The changes provide new entities, such as split-off peptides or formed enzyme inhibitor complexes, and changes in concentrations of components in the case of reactive synthesis. In blood we can measure the concentration of released reaction products of recent or ongoing action, and we will detect (some of) the effects on cellular release and reactive synthesis. We will not see the components that are and remain tissue bound.

There are increasing opportunities to detect low levels of reaction products of hemostasis activation, including the use of special monoclonal antibodies. It becomes further clear from recent reports that the concept of continuous low-grade turnover in these systems, as originally proposed by Astrup,[2,59] holds true and that analysis of this low-grade action at several levels of the cascades is possible. The first advantage of this approach in laboratory diagnosis is that the level of reaction products indicates the real action in the system. The assay of blood levels of proenzymes, cofactors, and inhibitors only provides us with an estimate of the potential of the system. The effects of the potential and its changes always require interpretation with our knowledge about the system and its mechanisms, and this knowledge is far from complete. Second, the evaluation of reaction products solves part of the problem that hemostatic processes are primarily localized and laboratory diagnosis is limited to the study of systemic blood samples. The reaction products provide information about all local events and indicate whether the locally released or bound factors have had effects. A remaining restriction is that the reaction products only provide an averaged and diluted message and do not provide an answer about the localization of the action. However, this latter aspect might also be advanced further in the future by using techniques of local sampling, sampling at several places, and occlusion of segments.[60,61]

It is advocated to analyze further the effects of the use of drugs such as oral contraceptives by evaluation of not only the changes in variables of the potential of the hemostatic systems, but specifically also changes in the parameters of the action of these systems. Some data on circulating reaction products can be found in these proceedings. The data on the prognostic value of levels of reaction products for thrombotic and cardiovascular diseases are still very limited. An interesting option has been presented by Owen et al.,[62] who showed for the postoperative period that the ratio of reaction products from coagulation and fibrinolysis was increased preceding deep venous thrombosis. This indicates that as proposed by Nossel,[63] ratios of action parameters of coagulation and fibrinolysis may be informative of the balance between the systems and of deviations in the balance.

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Interrelations between carbohydrates, lipids, and the hemostatic system in relation to the risk of thrombotic and cardiovascular disease

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Metabolic diseases, such as obesity, impaired glucose tolerance, type I and type II diabetes, hypercholesterolemia, and hypertriglyceridemia, are among the main risk factors for the development of atherothrombosis. Various abnormalities of the hemostatic system (platelet hyperaggregability, hypercoagulability, and hypofibrinolysis) have been described in all these situations. The individual effect of each of these diseases on the hemostatic system is difficult to evaluate because these states are often associated in the same patient and the treatment of one can benefit the others. Therefore it may be queried if a common abnormality of these pathologic states might explain their impact on the cardiovascular system. We have been interested by hyperinsulinemia, which is observed in obesity, impaired glucose tolerance, type II diabetes, and hypertriglyceridemia, and we have shown a very strong correlation between plasma insulin, body mass index, triglyceride levels, and one of the main inhibitors of the fibrinolytic system, plasminogen activator inhibitor-1. Partial correlation analysis showed that only the correlation between insulin and plasminogen activator inhibitor-1 was independent. Therefore a high plasma insulin level could be responsible for elevated levels of plasminogen activator inhibitor-1, which by inducing an hypofibrinolysis, could play a role in the deposition of fibrin and the development of atherothrombosis. The description of some interelations between metabolic diseases and hemostasis is satisfactory but does not exclude specific effects of these diseases on hemostasis, such as glycation of the coagulation and fibrinolytic factors in diabetes or toxic action of lipoprotein on endothelial cells in hyperlipoproteinemia. (AM J OBSTET GYNECOL 1990;163:313-5.)

Key words: Insulin, carbohydrate metabolism, lipid disorder, hemostatic system, cardiovascular disease

Carbohydrate and lipid disorders are among the main risk factors for the development of atherothrombosis. Various abnormalities of the hemostatic system have been described in all these disorders and may play a role in the initiation of the atheromatous lesion or its complication. However, the individual effect of each of these metabolic disorders on the hemostatic system is difficult to evaluate because these states are often associated in the same patient and the treatment of one can benefit the others.

Carbohydrate and lipid disorders are among the main risk factors for the development of atherothrombosis

Disorders of the glucose metabolism include mainly types I and II diabetes and impaired glucose tolerance and may be extended to increased calories storage, that is, obesity, especially when the fat distribution is oriented through the upper part of the body (abdominal or android obesity) and also to other insulin-resistant situations, the importance of which is now well recognized. Lipid disorders include increased plasma concentrations of triglycerides and low-density lipoprotein (LDL) cholesterol, which is often accompanied by a concomittant absolute or relative decrease in high-density lipoprotein cholesterol.

Various abnormalities of the hemostatis system have been described in all these situations.

Carbohydrate disorders are accompanied by platelet hyperactivity, with an increase in plasma von Willebrand factor, hypercoagulability with increased fibrinogen and factor VII level,[1] and hypofibrinolysis with increased plasma concentration of plasminogen activator inhibitor-1 (PAI-1).[2] At the vessel wall level, a proliferation of smooth muscle cells, an increase in lipid synthesis and deposition, a thickening of the basement membrane, and glycation of collagen have been reported.[3] Admittedly, these abnormalities are mainly due to the effects of hyperglycemia and advanced glycated end products[3] on the one hand and to the effects of hyperinsulinemia on the other.[4]

Lipid disorders are also accompanied by platelet hy-

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peractivity, hypercoagulability with increased factor VII,[5] and hypofibrinolysis with increased PAI-1.[6, 7] At the vessel wall level, an accumulation of lipid-filled foam cells is found.[8] The role of increased LDL cholesterol and apolipoprotein B, as well as the decrease in HDL cholesterol and apolipoprotein A_1, is now well established, and the toxic effect of oxydated lipoprotein on endothelial cells has been demonstrated.

Carbohydrate and lipid disorders are very often associated in the same patient and the treatment of one of them can benefit the others

More and more importance is presently given to abnormalities in insulin action and secretion. Reaven[9] proposed that insulin resistance is the common cause of several abnormalities, which he grouped under the term "syndrome X," and which includes the following: (1) android obesity, hyperinsulinemia, impaired glucose tolerance, and type II diabetes; (2) increased triglyceride and very low–density lipoprotein, increased LDL cholesterol, and decreased HDL cholesterol; and (3) hypertension.

Several intervention programs are able to decrease insulin level, such as diet in overweight persons, which improves glucose uptake by the periphery, an exercise training program that increases the number of insulin receptors, and antidiabetic drugs, such as biguanides, which improve insulin sensitivity. All these interventions[10, 11] can in parallel decrease more or less insulin, triglycerides, and LDL cholesterol, and increase HDL cholesterol.

Some interrelations exist between carbohydrate, lipid, and hemostatic disorders

Hypofibrinolysis favors the deposit of intravascular fibrin. Fibrinolysis is regulated through activators and especially inhibitors, the main one of which is PAI-1.[12] The plasma level of this inhibitor appears to be an independent risk factor for myocardial reinfarction in previously infarcted men <45 years old.[13]

It has been shown that plasma concentration of PAI-1 is increased in these patients[14-16] and patients with hypertriglyeridemia.[6, 7] We have also recently observed a close relationship between low fibrinolytic activity, high PAI-1, and high fasting plasma insulin levels in various populations: normal subjects,[14] premenopausal obese women,[15, 16] noninsulin-dependent diabetic subjects,[17] and patients with angina pectoris.[18] In all these studies the independent correlation coefficient between PAI-1 and insulin was around 0.6. Partial correlation analysis showed that triglyceride level or body mass index was no longer correlated with PAI-1 level after adjustment for insulin.

Furthermore, interventions to reduce plasma insulin level (and resistance), such as fasting[14, 19] or metformin administration,[11] induced a decrease in PAI-1 level. The hypothesis that insulin level regulates PAI-1 level is supported by the fact that insulin stimulates PAI-1 synthesis by liver cells in vitro.[20] Therefore high plasma insulin levels could be responsible, through direct action on liver synthesis, for elevated plasma triglyceride and PAI-1 levels. By inducing hypofibrinolysis, the latter could contribute to the pathogenic role of hyperinsulinemia. The normalization of insulin levels can be accompanied by the normalization of the lipid pattern and also PAI-1 level, that is, the suppression of one of the main hemostatic risk markers for myocardial infarction.[18]

Carbohydrate and lipid disorders also have specific effects on hemostasis and vessel wall

The description of some interrelations between metabolic diseases and hemostasis is satisfactory but does not exclude the specific effect of these diseases on hemostasis. In diabetes, glycation of proteins is an important pathogenic phenomenon. The glycation of hemostasis factors decreases their activity, that of LDL renders them more pathogenic and potentiates lipid accumulation in vessel wall, and that of collagen and basement membrane increases the trapping on von Willebrand factor, which favors platelet adhesion.[3] In lipid disorders, it is observed that oxydated LDL has a toxic effect on endothelial cells.[8]

In conclusion, both hyperglycemia and hyperlipoproteinemia per se modify the hemostatic milieu favoring the development and clinical complications of atherothrombosis. However, carbohydrate and lipid disorders are frequently associated, one leading to a potentiation of their impact on the vessel wall. Furthermore some abnormalities commonly observed in both these types of disorders, especially insulin resistance and excess, may explain the association of carbohydrate and lipid disorders as risk factors for atherothrombosis in epidemiologic studies.

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Why do we need pharmacokinetic studies?

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Data on the fate of sex steroids in the human organism, such as absorption, distribution, total clearance, and elimination routes, are necessary to understand and predict drug action. However, except for a few exceptions, such data are sparsely available. It is necessary to apply several approaches (descriptive, mathematic, and analytic) to describe variability and dose-response correlations, all of which are important for individualized treatment, and therefore of therapeutic relevance. In addition, such data are now unavoidable requirements for the evaluation of safety, efficacy, and quality performed by the regulatory authorities. Therefore human kinetic information is an integral part of the knowledge that forms the basis for any treatment with sex steroids. (Am J Obstet Gynecol 1990;163:316-8.)

Key words: Pharmacokinetics, dose response, variability, sex steroids

The question, "Why do we need pharmacokinetic studies?," is not easily answered whether it concerns sex steroids or any other preparation, and particularly not if seen in a clinical context. However, to address the problem in general, it is necessary to discuss some details of the pharmacokinetic universe.

Definition

While pharmacodynamics are characterized as the action of a drug in the organism, pharmacokinetics deal with the fate of a drug. However, a more operational description of pharmacokinetics is all the processes that determine the concentration of the active substance at the receptor site. This definition implies the connection with pharmacodynamics, without which kinetics may easily develop into a nonclinical playground.

Study approach

To obtain the kinetic characteristics of a drug, several types of studies are needed. The usually overlapping approaches may be classified into the following three basic ones: (1) *The descriptive approach,* by which all the processes involved are described, for example, how the absorption, distribution, and elimination take place and how the different organs and physiologic conditions influence these processes; (2) *the mathematic approach,* which includes calculations of compartments and rate constants, generation of models, and other types of "pharmacomathematic" exercise; and (3) *the analytic approach,* which tries to analyze the generated data in the context of other pharmacologic and clinical information.

The unifying concept is to explain and predict drug action in the human body. All three approaches are based on the measurements of concentrations in body fluids of the parent compound and its metabolites, most often by establishing plasma concentration/time curves. Therefore the value of such studies is heavily dependent on analytic assays that require a high degree of sensitivity, reproducibility, and specificity.

Parameters and data

Much uncertainty seems to exist about which pharmacokinetic parameters are essential. Table I shows what generally is required, but for more information, recent handbooks must be consulted.[1]

It would be of interest to see how much kinetic data on sex steroids are actually available in the literature. In most recent source of such information,[2] data on clearance, T½, V_d, and protein binding are given for only ethinyl estradiol, levonorgestrel, medroxyprogesterone acetate, and norethisterone. Even in the original kinetic studies, little data exist, at least compared with other groups of drugs. The paucity of information is striking.

Variability

Pharmacokinetic data are usually presented as an average of results from a studied population.[3-5] Naturally, such general information is important for the common characterization of the drug in question but cannot be used to predict, for example, plasma concentrations in individual patients. A range is often of greater interest

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than a mean value, and kinetic data should therefore include information on the variability between individuals.

For most drugs, the variability in kinetic parameters is more than 10-fold, even if the study population is quite homogenous and the dose is corrected for body weight. Basically, this can originate from variability in absorption and from differences in the metabolizing capacity of the liver caused by genetic or environmental factors. Presystemic metabolism seems to be an important determinant for the plasma levels of progesterone.[6] On the basis of individual kinetic data, it may be possible to sort out such factors. In addition, intraindividual variability might be large (see Fotherby, this supplement).

The dose-response concept

As emphasized, kinetic data only have a meaning when related to pharmacodynamic data. The pharmacologic way of expressing this is by dose-response curves, in which the dose may be substituted by plasma concentrations or other kinetic parameters. To generate meaningful and relevant concentration-response curves in patients is an extremely difficult task and therefore often neglected. However, if the concept became better understood, more energy would be put into this work. For sex steroids, only a few, if any, such human dose-response curves exist. This is also related to the difficulty in grading the effect parameter, although this may be overcome by the use of the percentage of "failures/successes" related to plasma concentration. However, both measuring and grading the effects are still the main obstacles for setting up reliable dose-response curves,[7, 8] and very sparse kinetic information makes this even more problematic. Another important use of dose-response curves is that they are necessary for meaningful comparisons between analogous drugs.

Regulatory requirements

The basic idea in drug regulation is that only drugs for which safety, efficacy, and quality have been evaluated—and found acceptable—are released for general use. The requirements should, of course, reflect profesional thinking and clinical relevance. Kinetic information must be presented for the evaluation of both safety and efficacy, because it will be required for most drugs to estimate toxic plasma concentrations and minimum plasma levels for efficacy. This means that kinetic studies should not be limited to healthy volunteers but be extended to relevant patient categories including risk groups, such as renal and hepatic insufficiency, and old age.

Today drug regulation is increasingly involving demands on the conduct of clinical trials. In Europe rules for good clinical (research) practice—the so-called Good Clinical Practice rules—will be the foundation of the authorities' future demands regarding trials of new drugs,[9] as in the United States.

Table I. Pharmacokinetic parameters required

Characteristics	*Parameter*
Absorption:	Absorption fraction (F), T_{max}, C_{max}
Distribution:	V_d, protein binding
Elimination:	Route, $T^1/_{2\beta}$, Cl_{tot}, pattern of metabolites, saturation phenomena
Steady-state:	Area under the curve (e.g., $AUC_{24\ hr}$), therapeutic plasma concentration range
Special features:	Kinetic interactions, influence of hepatic/renal insufficiency and age, autoinduction, and active metabolites

Therapeutic relevance

As previously stated, it should also be possible to use data from pharmacokinetic studies in humans as a prognostic instrument. Without this objective, pharmacokientics may be reduced to a sophisticated, academic exercise and, therefore, ethically questionable. Only a few examples within sex steroids exist, but to demonstrate the concept of the beneficial use of plasma concentrations, an example from cytostatics will be given. Methotrexate plasma levels were used to predict therapeutic outcome,[10] and it was found that patients with levels above a discriminating limit had a much greater chance of remission despite the fact that the same dose was given. This can, of course, be developed into a regular therapeutic drug monitoring system, but even without it, this line of thinking could be applied to existing data on sex steroids.[5] Therefore it would be a reasonable question whether such data could be used as a predictor of therapeutic outcome. Some efforts have been made in the treatment of breast cancer with medroxyprogesterone.[11] Furthermore, some data for prophylactic treatment of osteoporosis[12] may eventually be used in this connection. Finally, the induction of estrogen metabolism by phenobarbital or rifampicin should be better investigated in terms of kinetic data to define special risk groups, that is, those who lose the contraceptive effect because of this drug interaction.

In conclusion, the response to the question, "Why do we need pharmacokinetic studies?" is as follows: (1) A general characterization of the drug in humans includes kinetic information. (2) An estimation of the kinetic contribution to the variability of drug response is essential both between and within individuals. (3) Meaningful dose-response curves must be based on pharmacokinetics to design optimal dose regimens and to compare analogous drugs. (4) Regulatory authorities require kinetic data for a thorough evaluation of safety,

efficacy, and quality. (5) General measures may be developed on basis of kinetic studies to predict the outcome of a given drug treatment in individual patients on a safer basis. (6) Finally, sex steroids constitute no exception to these requirements.

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Selected aspects of the pharmacokinetics and metabolism of ethinyl estrogens and their clinical implications

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Careful studies in an adequate sample of subjects show a very marked degree of variability in the pharmacokinetics of ethinyl estradiol—specifically, in parameters such as area under the curve, half-life, and time to peak. This variability is seen in differences between different populations, as well as from one individual to another. These studies also show variability in area under the curve and other parameters in the same person from time to time. Such differences may equal or exceed the differences between low dose (35 μg) and high-dose (50 μg) formulations. The levels of plasma ethinyl estradiol produced by a 50 μg dose of mestranol are similar to those from 35 μg of ethinyl estradiol. Thus a high-dose pill may be no higher than a low-dose pill if the nature of the estrogen is not kept in mind. Qualitative differences in the oxidative metabolites of estrogens may be of significance with respect to oncogenic potential. (Am J Obstet Gynecol 1990;163:318-22.)

Key words: Ethinyl estrogens, area under the curve, mestranol, ethinyl estradiol, pharmacokinetics

Although the pharmacokinetics of ethinyl estrogens have been studied intensively for more than a decade,[1] many unresolved problems of practical interest, as they affect contraceptive effectiveness, remain to be examined.

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Table I. Pharmacokinetic parameters for ethinyl estradiol 3-sulfate and 17-sulfate

Parameter	*EE/3-sulfate*	*EE/17-sulfate*
$t_{1/2}$ (IV) (hr)	8.4	9.3
AUC_{0-24} (ng hr/ml IV)	4.6 ± 0.5	16.9 ± 3.4
Bioavailability (%)	50 ± 13	23 ± 5
Conversion to free EE (%)		
IV	13.7	3.4
po	20.7	11.7
Comparison		
E_1 sulfate→E_1 IV	14	

From Goldzieher JW, et al. Steroids 1988; 51:63.

EE, Ethinyl estradiol; *IV*, intravenous; *po*, by mouth; *AUC*, area under the curve; E_1, estrone.

Table II. Interindividual variability

Parameter	*Mean ± SD*	*Range*	*CV (%)*
Norethindrone			
1/35 AUC_{0-24} (ng · hr/ml)	72.8 ± 23.4	19.8 – 149	55.6
1/50 AUC_{0-24}	87.9 ± 29.1	15.6 – 197	57.4
1/35 C_{max} (ng/ml)	14.0 ± 5.4	4.7 – 25.6	
1/50 C_{max}	17.1 ± 7.7	4.8 – 35.9	
Ethinyl estradiol			
AUC_{0-24} (pg · hr/ml)	1036 ± 483	284 – 2498	47
C_{max} (pg/ml)	174 ± 67	55 – 311	39
Ethinyl estradiol from mestranol			
AUC_{0-24}	963 ± 544	215 – 2122	57
C_{max}	175 ± 72	67 – 391	41

From Brody SA, et al. Contraception 1989; 40:269.
CV, Coefficient of variation; *AUC*, area under the curve; C_{max}, maximum plasma level.

Population differences

It has been established by the work of Fotherby et al.,[2] Goldzieher et al.,[3] and others that the pharmacokinetics of ethinyl estrogen, particularly blood levels and consequent area under the curve, differ from one population to another despite correction for body weight. The origin of these differences, whether they are caused by dietary, ethnic, or other factors, is unknown. They are not, however, merely differences in rates of gastric absorption or renal excretion. Studies comparing women in Nigeria, Sri Lanka, and the United States have shown that the pattern of steroid conjugation to sulfates and glucuronides, which is primarily a hepatic function, varies from one locality to another.[4] Moreover, analysis of urinary steroids shows qualitative and quantitative differences in oxidation of the steroid molecule at the 2, 6, and 16 positions. The origin of these differences in enzymatic attack on the steroid molecule has not been investigated except to show that they are present on initial exposure of the subject to these agents and remain essentially unchanged after many months of contraceptive use.

Circulating ethinyl estrogen sulfates

The sulfates of estrogens circulate in the blood in much higher concentration than the free steroid itself, often by an order of magnitude. Studies in baboons have examined the kinetics of the ethinyl estradiol sulfates[5]; more recently the kinetics and bioavailability of the 3- and 17-sulfates have been examined in human volunteers.[6] The statistics of interest are shown in Table I. The half-lives of both conjugates are not appreciably different from the half-life of ethinyl estradiol itself; consequently, the notion that these sulfates persist for long periods and act as a potential reservoir for the regeneration of free ethinyl estradiol cannot be maintained. Although the two sulfates show large differences in area under the curve and bioavailability, the most significant finding of practical interest is the rate of conversion to free, circulating ethinyl estradiol. After oral administration of the 3-sulfate, only about 20% appears as free ethinyl estradiol in the blood; the 17-sulfate produces about half this amount. This does not augur for a clinically important role that might help "tide over" spells of low plasma ethinyl estradiol levels resulting from noncompliance.

We have also observed that individual variation in plasma total ethinyl estradiol sulfate levels shows the same large spread as has been observed by many investigators for free ethinyl estradiol. This is true for the conjugates resulting from the oral administration of the 3- or the 17-sulfate.[7]

Bioavailability

Although it is tempting to assume that preparations of similar hormone content made by various major manufacturers are identical in bioavailability, the published comparative data are very scanty. We have recently analyzed the pharmacokinetics of three 1 mg norethindrone/35 μg ethinyl estradiol and three 1 mg norethindrone/50 μg mestranol formulations; these data have been published.[6] Comparisons of plasma level data for the three ethinyl estradiol preparations show that they are indistinguishable based on mean values, standard deviations, and highest and lowest individual plasma patterns. The three mestranol-containing agents are equally similar, and there are no statistically significant differences in area under the curve.

Conversion of mestranol to ethinyl estradiol

Of great interest was a comparison of ethinyl estrogen levels obtained from the administration of 50 μg of mestranol compared with the direct administration of 35 μg of ethinyl estradiol. This issue of conversion of mestranol to ethinyl estradiol has been discussed repeatedly in the literature and has often been obfuscated by reference to the interconversion in rodents, which is quite different from that in humans. In any event, the administration of 50 μg of mestranol resulted in an average area under the $curve_{EE}$ of 963 ± 544, whereas that from 35 μg of ethinyl estradiol produced an area under the curve of 1036 ± 483 (Table II). In

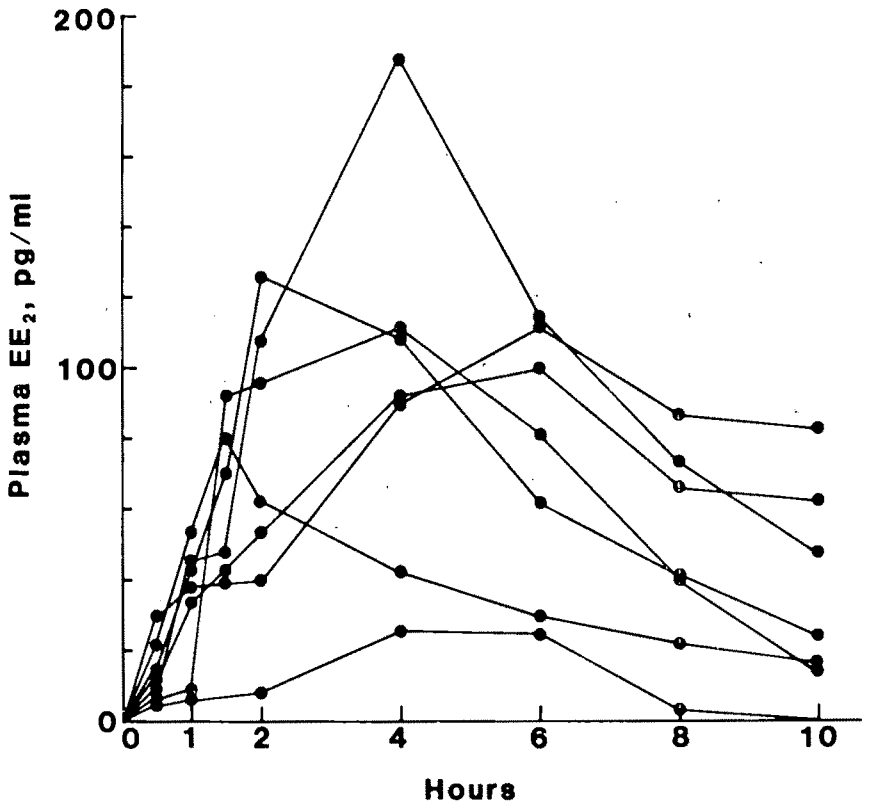


Fig. 1. Plasma ethinyl estradiol levels after single-dose administration. The great variability, despite efforts to eliminate external variables, is noteworthy. (From Goldzieher JW. Pharmacology of contraceptive steroids: a brief review. AM J OBSTET GYNECOL 1989;160:1260-4.)

Table III. Intraindividual variability (three single-dose trials)

	CV (%)	*Range (%)*
Norethindrone		
1/35	17.4	−79 → +134
1/50	36.5	
Ethinyl estradiol		
1/35	41.0	−7 → +92
1/50	42.0	

From Brody SA, et al. Contraception 1989; 40:269.
CV, Coefficient of variation.

other words, 35 μg of ethinyl estradiol is a "stronger dose" than is 50 μg of mestranol. In truth, the difference is not statistically significant because of the extremely wide range of interindividual variation. However, epidemiologic comparisons of 50 μg oral contraceptives with "low-dose" 35 μg oral contraceptives are meaningless unless the estrogens are kept straight.

Inter- and intraindividual variability

Interindividual variability has often been documented but seldom quantitated in sufficiently large groups. In the study of Brody et al.,[6] 24 patients received the 35 μg ethinyl estradiol formulations and 27 received the 50 μg mestranol agents. The details of interindividual variation are shown in Table II in standard deviation, coefficient of variation, and extreme range of values. Similar results have been previously published for ethinyl estradiol (Fig. 1) and ethinyl estradiol sulfates (Fig. 2). Norethindrone (Table II) shows comparable findings as might be expected because it also undergoes enterohepatic recycling.

The study of Brody et al.,[6] which examined the pharmacokinetics of three identical formulations by different manufacturers, showed them to be bioequivalent. This observation permitted an insight into intraindividual variation, since all three brands were tested in each individual, at the same time of the cycle, in three consecutive months. Only a single dose was administered in each cycle. There are virtually no published data on intraindividual variation, and the extreme degree of variability came as a considerable surprise. The ranges and coefficients of variation are given in Table III and individual examples in Table IV. Extreme values ranged from −79% to +134% of the mean of the three determinations per individual.

The findings of such a range of inter- and intraindividual variability have important clinical implications. It is quite clear that plasma ethinyl estradiol levels

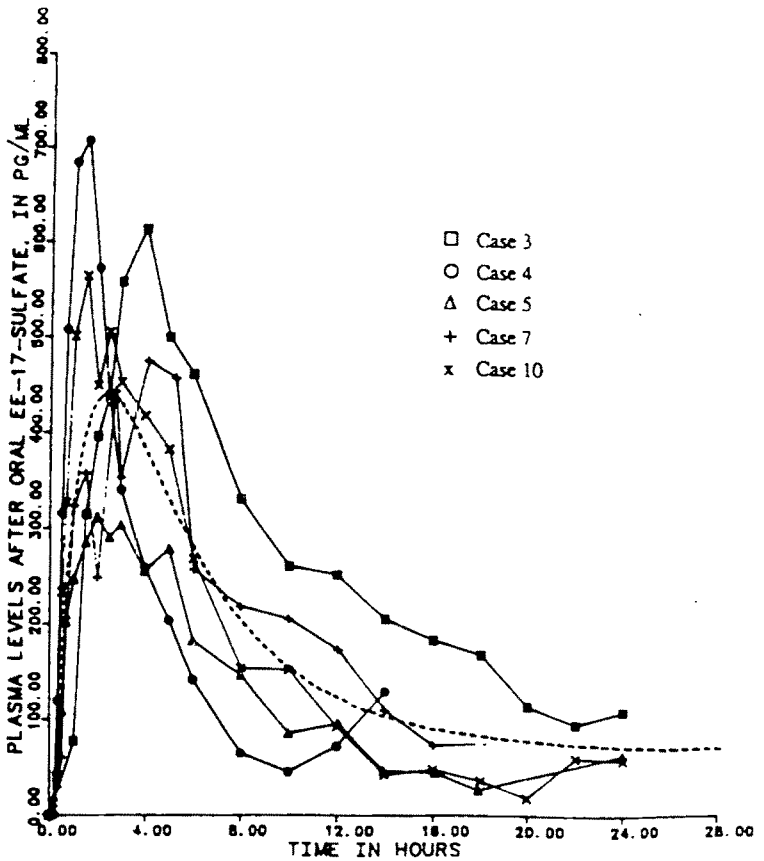


Fig. 2. Plasma levels of ethinyl estradiol after single-dose oral administration of ethinyl estradiol 17-sulfate in five individuals. *Dotted line* represents mean value. (From Goldzieher JW, et al. Human pharmacokinetics of ethynyl estradiol-3-sulfate and 17-sulfate. Steroids 1988;51:63-79.)

Table IV. Representative plasma AUC_{0-24} for repeated trials in same individuals

	Ethinyl estradiol			*Norethindrone*		
Subject No.	*Norcept*	*Ortho-Novum*	*Norinyl*	*Norcept*	*Ortho-Novum*	*Norinyl*
			1 + 35 EE formulations			
2	1002	431	855	29.2	23.1	49.3
9	252	499	569	32.2	55.7	46.8
12	1892	637	1390	79.7	77.2	91.7
13	1563	539	934	98.9	169.9	127.2
20	657	1594	2122	90.3	86.3	88.0
			1 + 50 ME formulations			
104	215	1230	658	30.3	73.7	120.5
106	1355	854	1080	175.0	33.9	15.6
3	768	963	696	109.8	86.6	31.6
16	1033	839	818	58.5	38.4	109.0
25	433	289	331	68.1	62.1	62.5

EE, Ethinyl estradiol; *ME*, mestranol.

engendered by 35 μg ethinyl estradiol may be indistinguishable from those produced by 50 μg in another person; thus these gravimetric values give a false sense of dosage discrimination. This accounts for the well-established observation that the same dose may produce overdosage effects (e.g. nausea) in one person and underdosage effects (e.g. breakthrough bleeding) in another. It also points out that efforts at fine-tuning dosage to minimize adverse effects of either variety are not going to succeed except "on the average." Finally, comparisons of the effects of one dose with another will have to take account of a broad degree of overlapping if the effects in question are related to the plasma kinetics of the compound.

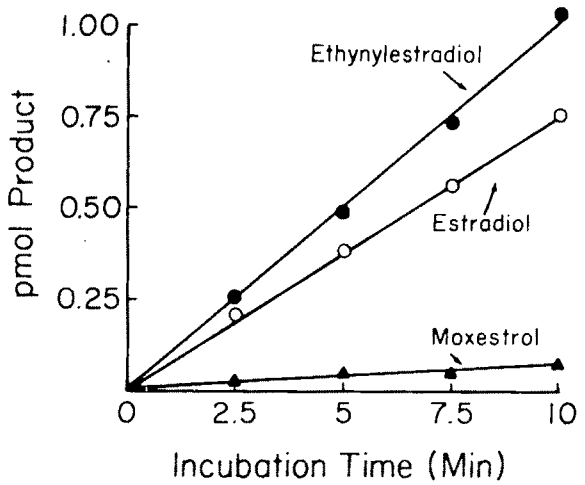


Fig. 3. Concentration of oxidative metabolites of various ethinyl estrogens after incubation with a cell population in vitro. (From Purdy RH, Goldzieher JW. Intervention in the aging process, part A. Qualitative, epidermiology and clinical research. New York: Alan R Liss, 1983:247.)

Qualitative differences in ethinyl estrogens

Finally, I will comment on qualitative differences in the ethinyl estrogens over and above the question of the metabolic conversion of mestranol to ethinyl estradiol. Another compound, moxestrol, the 11β-methoxy derivative of ethinyl estradiol, is available in some countries. It is approximately 10 times as potent as ethinyl estradiol itself, which means that 2 to 3 μg, together with a progestin, should be contraceptively effective. However, this is merely a question of relative potency. What is the most interesting feature of this compound is its activity (or rather inactivity) in promoting neoplastic transformation of certain cell clones. These data have been published[8] but have not been widely recognized for their importance. Briefly, exposure of certain cell clones to estradiol, ethinyl estradiol, stilbestrol, etc., causes formation in vitro of foci of transformed (neoplastic) cells, as shown in Table V. Moxestrol, although estrogenically active, did not produce cell transformation. The mechanism of this effect has been elucidated.[9] All the estrogens that can produce this neoplastic transformation can be oxidized to catechols or epoxides, structures that are known to play a role in the carcinogenic effects of polycyclic hydrocarbons. As shown in Fig. 3, the incubation conditions used produced linear increases in these oxidative metabolites with estradiol or ethinyl estradiol but not with moxestrol. The 11β-methoxy group appears to interfere with this type of oxidative attack. One cannot, of course, extrapolate from this effect to the oncogenic role of estrogens in humans, but it assuredly opens a new avenue of exploration for the development of potentially "safer" estrogens.

Table V. Neoplastic transformation of Balb/c 3T3 A-31-1-13 subclone by estrogens

Chemical	*Concentration*	*Total type III transformed Foci on ___ of ___ dishes*
DMSO control	0.25%	0 on 0 of 15
Ethinyl estradiol	25 μmol/L	41 on 14 of 50
Moxestrol	25 μmol/L	0 on 0 of 15

From Purdy et al. Catechol estrogens. New York: Raven Press, 1983:123.

DMSO, Dimethyl sulfoxide.

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Pharmacokinetics of gestagens: Some problems

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Various approaches to studying the pharmacokinetics of gestagens and the factors that influence derivation of the parameters are described with levonorgestrel used as an example. Published studies of the pharmacokinetics of levonorgestrel are reviewed, and new information is presented regarding intra- and intersubject variation. Differences between various formulations of levonorgestrel are apparent when the formulations are compared in the same subjects. There is also a marked difference in the parameters when derived under single-dose or steady-state conditions. The role of sex hormone–binding globulin in the metabolism of levonorgestrel is questioned. Large intra- and inter-subject variations in the parameters exist, and a subject may show a large month-to-month variation when one levonorgestrel formulation is used and smaller variations when another formulation is used. This wide variability in the pharmacokinetic parameters, problems that arise in the derivation and interpretation of the parameters, the biologic significance of most of these parameters, and their lack of correlation with pharmacodynamic responses severely limit the usefulness of pharmacokinetic studies of the gestagens. (AM J OBSTET GYNECOL 1990;163:323-8.)

Key words: Pharmacokinetics, gestagens, oral contraceptives, variability, sex hormone–binding globulin

The comments on pharmacokinetics presented in this article relate only to the gestagens used in oral contraceptives. The pharmacokinetics of contraceptive steroids is a specialized topic, as evidenced by the fact that most textbooks and monographs on pharmacology denote little if any attention to this area. The pharmacokinetics of the gestagens show many facets not seen with most other drugs, and these lead to many problems in both the derivation and interpretation of the pharmacokinetic parameters.

There are four main approaches to the pharmacokinetic analysis of serum drug concentrations: (1) Simple description describes the changes in serum drug concentrations with time and allows the determination of the rate of absorption and bioavailability, the rate of elimination of the drug, and the steady-state concentrations. (2) Compartment modeling derives equations based on the assumption of one, two, or more body compartments throughout which the drug is distributed and relates changes in serum drug concentrations with time. The assumed compartments may have no physiologic meaning, and as the number of postulated compartments increases, the mathematic complexity increases so that a model based on more than two compartments becomes difficult to deal with. (3) Iterative curve fitting makes no assumptions about compartments, but by computer analysis attempts to derive the equation that best describes the changes in serum drug concentrations with time. Such equations will usually be complex and may be difficult to interpret. (4) Systems dynamics considers the body as a system with a large number of subsystems; the flux of the drug through the various subsystems is determined by positive feedback.[1] This approach has not yet been widely applied and not at all so far to steroids.

Each approach has it advantages and disadvantages and that most appropriate for the problem under investigation must be chosen. Compartment modeling, which uses a two-compartment open model, has been widely used for the gestagens, but the simple descriptive approach will give the clinician, although maybe not the pharmacologist, most of the information required. This information will usually be as follows: (1) how rapidly the gestagen is absorbed (the time required [T_{max}] to reach peak concentration in blood); (2) an indication of bioavailability, usually by assessment of the area under the serum concentration–time curve (AUC); (3) how rapidly the gestagen is eliminated from the body, usually by determining the half-life of elimination; this widely used parameter (the time required for the serum gestagen concentration to decrease by 50%) may, however, often be misleading because it is determined by two other parameters, the apparent volume of distribution and clearance, and these may change considerably, denoting marked changes in the metabolism of the gestagen without any changes in the half-life of elimination. (This aspect is discussed in more detail in a forthcoming article.[2]) However, the

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Table I. Half-life of elimination (hours) of LNG (values taken from published studies, for definition of "recalculated value," see text)

Formulation	*LNG 250, EE 50*	*LNG 150, EE 30*	*LNG 30*	*LNG 250, EE 50*	*LNG 1000*	*LNG 150, EE 30*	*LNG 150, EE 30*
Reference	9	10	11	11	11	12	3
n	5	5	5	5	5	9	24
Reported value (mean)	11.9	11.4	13.7	12.6	12.6	8.0	18.0
SD or range	1.7	1.3	8-23	10-19	9-20	3.2	8-43
Recalculated value	13.1	12.0	14.1	13.3	15.4	9.6	18.0

n, Number of estimates.

half-life of elimination has the advantage that it can be determined simply from the plot of serum gestagen concentrations against time; (4) the serum concentration under steady-state conditions, since this will be more relevant to the biologic activity of the gestagen than concentrations after a single dose. However, regarding the gestagens, steady-state conditions have not often been determined until recently.

Since these four parameters are the most often derived and useful ones, the factors influencing their determination and interpretation should be considered. Little difficulty usually arises in T_{max} and steady-state conditions so that only half-life of elimination and AUC will be discussed in more detail.

General considerations

Of the gestagens widely used in oral contraceptive formulations, levonorgestrel (LNG) will be mainly used as the example because it has the following advantages: (1) More information is available for LNG than for the other gestagens; (2) it does not undergo a first-pass effect so that complications that may arise as a result of metabolism in the gut or liver are avoided; and (3) most published studies have analyzed their data in a similar way in a two-compartment open model. One disadvantage, but one that is common to the other gestagens, is that most of the pharmacokinetic studies reported have involved only small numbers of subjects. Of the more than 17 papers concerned with serum LNG concentrations after administration of various oral contraceptives containing LNG, only two provide data for more than 10 study periods. Goebelsmann et al.[3] studied 24 women, and although only six were investigated by Dennerstein et al.,[4] sampling was performed during each of 3 months of treatment so that 18 sets of data were available per formulation used. All other studies include less than 10 and usually five or less subjects. Most studies have analyzed the data in a two-compartment open model. Although LNG has been used for illustrative purposes, the points considered are equally applicable to all other gestagens used in contraceptive formulations.

In determining half-life of elimination and AUC, factors that may need to be taken into account include the following: (1) the dose of the gestagen and the route by which it is administered; (2) the dose, if any, of estrogen with which it is administered; (3) the status of the subjects at the time blood sampling is performed; (4) the number of samples and the time period over which they are taken; (5) whether taken under steady-state or single dose conditions; (6) the procedures used for calculating the pharmacokinetic parameters; and (7) the reliability criteria of the method used to estimate the serum gestagen concentrations; this is particularly important with the low-dose formulations at the longer times after dosing since by 24 hours, serum concentrations in many subjects will be near the limit of sensitivity of the assay. This is important not only for the validity of the 24-hour concentration but also for determining whether this concentration is significantly different from that of samples taken later.

In almost all of the studies, sampling has not continued beyond 24 hours, and this may lead to an underestimate of half-life of elimination, particularly for gestagens with a long half-life of elimination (20 hours or more). In such studies half-life of elimination will include the "β-half life" but not the subsequent half-lives of compounds that do not follow the kinetics of a first-order reaction. Similarly, considerable errors may be encountered in determining the AUC. If sampling is terminated at 24 hours, AUC (0 to 24 hours) can be calculated by the trapezoid rule, but AUC (24 to ∞) may be significant for gestagens with a long half-life, and calculation of AUC (0 to ∞) by some suitable equation usually assumes, possibly erroneously, that the elimination rate for the period 24 hours to infinity does not differ from that for 0 to 24 hours.

Elimination of LNG

Published values for half-life of elimination of LNG are summarized in Table I. Most of the reported mean values are within a narrow range, although in three studies[3, 5, 6] considerably longer values were obtained. In one of these studies[3] the longer mean value may result from the larger number of subjects studied and consequently the larger range obtained; this range en-

LNG 750	*LNG 150, EE 30*	*LNG 250*	*LNG 250*	*LNG 250, EE 50*
13	6	5	4	4
6	6	6	18	18
12.0	25.1	26.4	—	—
4.8	21-35	7.0	—	—
13.9	14.5	14.9	19.3	30.0

compasses the values found in all other studies except that of Dennerstein et al.[4] The fivefold range for half-life of elimination shown in Table I agrees with the large variation reported for half-life of elimination of norethisterone,[7] and such a large variation appears to be a common finding with contraceptive steroids.[8] The longer values reported by Humpel et al.[5, 6] are more difficult to explain but they agree with the values calculated from data reported in Dennerstein et al.[4] In this latter study, six women were given either 250 μg LNG or 250 μg LNG with 50 μg ethinylestradiol (EE) daily for 3 months with blood samples being taken at 2, 8, and 26 hours after dosing on the last day of each treatment period. The subjects were randomized to the initial treatment and crossed-over after 3 months of use. From the serum LNG concentrations in the 8 and 26 hour samples, the approximate half-life of elimination was calculated. As shown in Table I, recalculation of half-life of elimination from published studies on the basis of the 8- and 24-hour serum concentrations gave values that, with the exception of two studies,[5, 6] were in good agreement with, although slightly higher than, values obtained from the investigators' pharmacokinetic analyses. Therefore the values calculated from the concentrations reported by Dennerstein et al.[4] appear to be valid. The values for each treatment month for each subject are shown in Table II.

In contrast with the other studies, the values in Table II provide information on half-life of elimination under steady-state conditions and within-subject variability. For some subjects (e.g., subjects 1 and 4, LNG 250 + EE 50; subjects 2 and 5, LNG 250) monthly variations were small, whereas for others (e.g., subjects 2 and 6, LNG 250 + EE 50: subjects 3 and 6, LNG 250) the variation was much wider. The mean intersubject variation was higher (47%) in women receiving LNG 250 + EE 50 than in women receiving LNG 250 (32%), but because of the wide range of these values, the differences would not be statistically significant. It is also of interest and importance that subjects may show a high variability when receiving one formulation and not when receiving the other (e.g., subjects 2 and 5). The intersubject variability for half-life of elimination in this study under steady-state conditions (two-

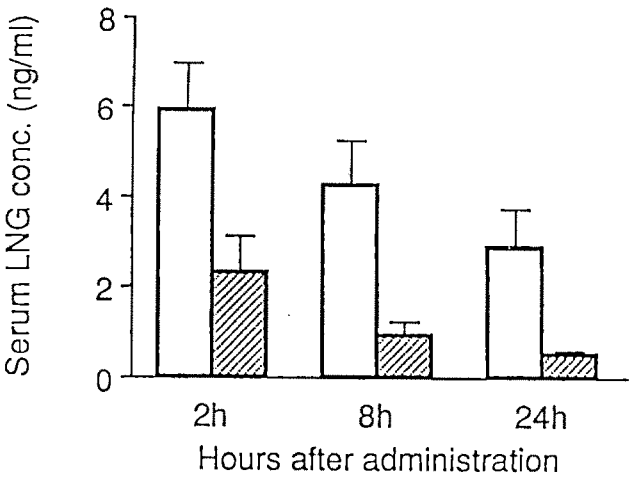


Fig. 1. Serum LNG concentrations in two groups each of six women receiving LNG formulations daily for 21 days □, Women receiving LNG 250 + EE 50; ▨, women receiving LNG 250. Values are the mean; *vertical lines* denote SD. (Data from Dennerstein et al.[4])

to threefold) is probably slightly lower than that observed in single-dose studies.

Bioavailability of LNG

Published values for bioavailability as measured by AUC are summarized in Table III. These values must be related to the dose of LNG, and when this is taken into account, there is reasonably good agreement between the mean values. However, the intersubject variability as shown by the values for SD and the range is high, particularly so in one study.[3] There is also wide intersubject variation with norethisterone,[7] and such large variations seem common to all contraceptive steroids.[8] The recalculated values in Table III refer to determinations of AUC based on serum LNG concentrations at 2, 8, and 24 hours published in the various studies and are calculated for comparison with values similarly obtained from serum concentrations at 2, 8, and 26 hours reported by Dennerstein et al. For most of the studies, this recalculated value is about 75% of the value obtained in the investigators' pharmacokinetic analysis. Therefore the calculation of AUC from the concentrations reported by Dennerstein et al. appears to have some validity. The values for each treatment month for each subject are shown in Table IV.

These values provide information on AUC under steady-state conditions and on within-subject variability. As for half-life of elimination, some subjects show only small month-to-month variations, whereas for others, this variability is much larger. The mean intrasubject variation was generally low (13.8%) in women receiving LNG 250 + EE 50 and significantly lower than that in women using LNG 250 (45.3%). The mean value for LNG 250 + EE 50 in this study (99.7%) is much higher

Table II. Half-life of elimination (hour) of LNG in a group of six women during each of 3 months of treatment with LNG, 250 μg + EE, 50 μg, or LNG, 250 μg, without estrogen (variation percent denotes percent variation of monthly values in relation to subject's mean value, variation ratio denotes highest monthly value divided by lowest monthly value)

Formulation	*LNG 250 + EE 50*						*LNG 250*					
Subject	1	2	3	4	5	6	1	2	3	4	5	6
Mo 1	22.5	54.0	27.0	20.8	37.8	45.0	16.2	16.4	28.7	18.8	18.6	17.2
Mo 2	22.8	36.0	35.4	19.8	23.6	20.1	19.6	16.0	16.8	17.3	17.4	27.3
Mo 3	28.5	31.8	23.5	18.0	20.1	52.7	15.1	19.4	17.3	23.7	15.9	26.3
Mean	24.6	40.6	28.6	19.5	27.2	39.3	17.0	17.3	20.9	19.9	17.3	23.6
Variation %	23.2	54.7	41.6	14.3	65.1	82.9	26.5	19.6	56.9	32.2	15.6	42.8
Variation ratio	1.3	1.7	1.5	1.2	1.9	2.6	1.3	1.2	1.7	1.4	1.2	1.6
Overall mean and range			30.0 (18.0-54.0)						19.3 (15.1-28.7)			

Table III. Bioavailability of LNG (AUC in ng/ml/hr) (values taken from published studies, for definition of "recalculated values," see text)

Formulation	*LNG 250, EE 50*	*LNG 150, EE 30*	*LNG 150, EE 30*	*LNG 150, EE 30*	*LNG 150, EE 30*	*LNG 750*	*LNG 250*	*LNG 250, EE 50*
Reference	9	10	12	3	6	13	4	4
n	5	5	9	24	6	6	18	18
Reported value (mean)	36.2	20.4	20.2	35.0	32.3	116	—	—
SD or range	12.8	3.0	7.8	9-120	13.7-48.8	41	—	—
Recalculated value	37.4	24.8	15.2	27.0	23.5	86.2	24.3	99.7

n, Number of estimates.

Table IV. Bioavailability (AUC in ng/ml/hr) of LNG (for details see legend to Table II)

Formulation	*LNG 250 + EE 50*						*LNG 250*					
Subject	1	2	3	4	5	6	1	2	3	4	5	6
Mo 1	89.2	106.3	134.0	68.1	107.6	96.0	37.7	20.6	15.4	27.5	28.8	25.7
Mo 2	78.4	82.0	149.5	73.4	102.8	101.8	21.7	17.3	36.9	22.1	22.4	25.9
Mo 3	88.6	112.5	134.1	67.9	96.4	106.2	18.8	12.9	34.3	17.0	24.4	27.8
Mean	85.4	100.3	139.2	69.8	102.3	101.3	26.1	16.9	28.9	22.2	25.2	26.5
Variation %	12.6	30.4	11.1	7.9	10.9	10.1	72.4	45.5	74.4	46.4	25.4	7.9
Variation ratio	1.1	1.4	1.1	1.1	1.1	1.1	2.0	1.6	2.4	1.6	1.3	1.1
Overall mean and range			99.7 (67.9-149.5)						24.3 (15.4-37.7)			

than that (36.2%) found by others[9]; this is probably because compared with the latter value the former is obtained under steady-state conditions. Also, again probably because the values in Table IV are obtained under steady-state conditions, the intersubject variation was lower than that seen in single-dose studies.

Role of sex hormone–binding globulin in LNG pharmacokinetics

LNG is known to bind to sex hormone–binding globulin (SHBG) with a greater affinity than other gestagens, and about 50% of the LNG in serum is bound to this protein.[2] The SHBG concentration in serum can be greatly increased by estrogen administration, and in several studies the higher levels of LNG in serum when the gestagen is given with estrogen compared with those when the same dose of LNG is given without estrogen have been attributed to binding of LNG to the increased levels of SHBG.[4, 11, 14] Examples of this phenomenon are shown in Figs. 1 and 2. In Fig. 2 it will also be noted that about 8 days are required to achieve steady-state levels of LNG. The mean value for half-life of elimination from the studies shown in Table I is 15 hours so that steady-state levels of LNG should have been attained in about 3 days. The rise in SHBG concentrations induced by estrogen occurs gradually from the first day of dosing until about day 10 when a plateau is reached,[15] and this has been used as further evidence that the slow attainment of steady-state levels of LNG is associated with the rise in serum SHBG concentrations. However, these suppositions appear untenable. Four studies of changes in serum

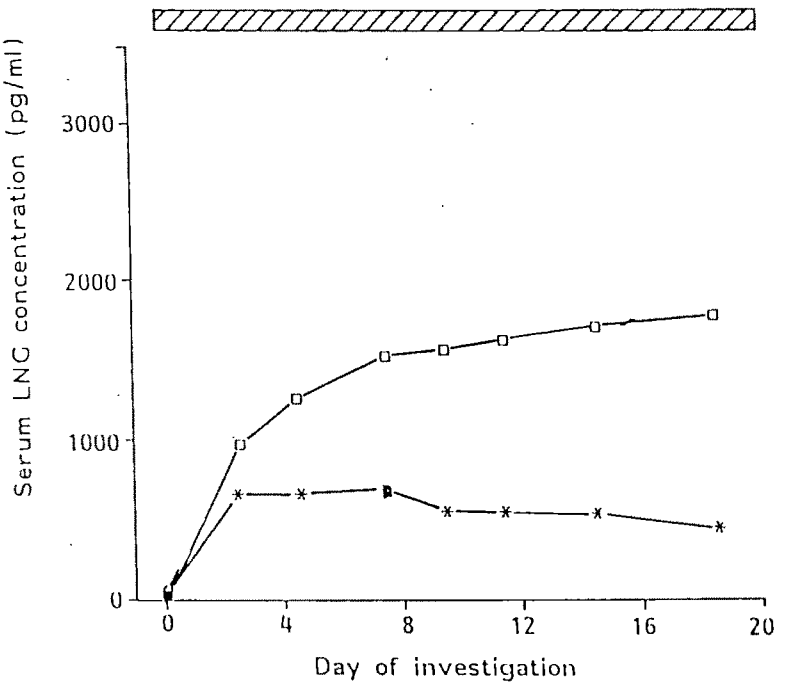


Fig. 2. Mean serum LNG concentrations in two groups each of six women receiving LNG formulations daily for 20 days □, Women receiving LNG 150 + EE 30; *asterisk*, women receiving LNG 150. (Data from Song Si et al.[15])

SHBG concentrations in women taking LNG 250 + EE 50 show *decreases* of from −8% to −36%, with a mean decrease of 24%. These small decreases are unlikely to be statistically significant, but they clearly demonstrate that there is no *increase* in SHBG levels with this formulation. At least 17 studies with LNG 150 + EE 30 report changes in SHBG varying from 0% to 75%. In those studies in which only a small increase was reported, this is unlikely to be statistically significant, but assuming that it is, the mean change in SHBG is a mere increase of 12%. Therefore the mechanisms responsible for the increase in serum LNG concentrations when the gestagen is administered with estrogen to values higher than those when the same dose is administered without estrogen must be independent of SHBG.

In conclusion, this article presents new information on the pharmacokinetics of LNG and provides the only data available on half-life of elimination and AUC under steady-state conditions and on intrasubject variability. Although there are considerable differences in the pharmacokinetics among the four gestagens (LNG, norethisterone, desogestrel, and gestodene) used in oral contraceptives,[2] the remarks about LNG are also applicable to the other three gestagens.

The month-to-month variability in half-life of elimination and AUC may be considerable (up to 250%) in the same subject, even though the estimates were made in 3 consecutive months with the subjects under fairly "basal" conditions. This variability limits the extent to which estimates of pharmacokinetic parameters, determined even under steady-state conditions at one point in time, can be extrapolated to other times. This is particularly important for drugs such as oral contraceptives that are used on a long-term basis, because over the period of use, changes in the subject's physiology and social habits may accentuate the "basal" monthly variations. Although only half-life of elimination and AUC were analyzed in this report, similar variability most likely occurs in other pharmacokinetic parameters, but the available data are too meager for any of the gestagens to perform a proper analysis. The intrasubject variability described here was, as expected, always less than the intersubject variability. Another important aspect of intrasubject variability is the absence of any correlation between the rate at which a particular subject metabolizes the gestagen and estrogen components of an oral contraceptive.[7]

Although it has been suspected that the pharmacokinetics of any gestagen may depend on the particular formulation administered, evidence to substantiate this has so far been very tentative because the intersubject variation is large in relation to the differences in pharmacokinetic behavior between the formulations. The results presented here show marked differences in half-life of elimination and AUC, and therefore presumably in the other parameters, between two formulations containing the same dose of LNG administered with or

without estrogen when these are compared in the same subjects. Since the dose of LNG in the two formulations is identical, since LNG is completely absorbed, and since it is unlikely that there is any difference in the rate of absorption, the marked difference between the two formulations in bioavailability as assessed by AUC, with that for LNG + EE being about four times that of LNG alone, may be artifactual. This may indicate that for oral contraceptives, measurement of AUC is not a valid indication of bioavailability unless this term is rigorously defined.

From the evidence available, it is not possible to decide firmly which of the two basic processes (volume of distribution or clearance) that determine half-life of elimination is responsible for the differences in half-life of elimination between the two formulations. Although serum SHBG concentrations show a small decrease with LNG + EE, the decrease is greater with LNG alone, and consequently there will be a greater decrease in the binding of LNG. This decrease in binding will increase volume of distribution, which will tend to lengthen half-life of elimination, and volume of distribution (LNG) should be greater than volume of distribution (LNG + EE), but the increase is unlikely to be more than twofold. Since the dose of LNG is the same in both formulations and AUC (LNG + EE) is about fourfold AUC (LNG), the apparent clearance for LNG will be about fourfold that of LNG + EE, and this will decrease half-life of elimination. Thus the twofold difference in half-life of elimination between LNG + EE and LNG appears to be due to a twofold lengthening of half-life of elimination resulting from an increase in volume of distribution in group LNG and a fourfold shortening of half-life of elimination in group LNG resulting from the fourfold increase in clearance.

The extent to which the intrasubject variation in pharmacokinetics affects the pharmacodynamic response is not known. It seems, however, that both the intra- and intersubject variability in pharmacokinetics is much greater than the pharmacodynamic responses, and if this is so, the question is raised of whether there is any correlation between the pharmacokinetics of the gestagens and their pharmacodynamic effects. At present any correlation is obscure.

This possible lack of correlation with biologic response, the wide inter- and intrasubject variability in pharmacokinetic parameters, the problems that arise in their derivation and interpretation, and the biologic significance of most of these parameters appear to limit severely the usefulness of pharmacokinetic studies of the gestagens.

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Protein binding of active ingredients and comparison of serum ethinyl estradiol sex hormone–binding globulin, corticosteroid-binding globulin, and cortisol levels in women using a combination of gestodene/ethinyl estradiol (Femovan) or a combination of desogestrel/ethinyl estradiol (Marvelon) and single-dose ethinyl estradiol bioequivalence from both oral contraceptives

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Results from two clinical pharmacokinetic studies are given. The first study was an observational study in oral contraceptive users who took either a combination of gestodene and ethinyl estradiol (pill A, Femovan) or desogestrel and ethinyl estradiol (pill B, Marvelon). A total of 69 women (39 receiving pill A and 30 receiving pill B) were evaluated to determine serum ethinyl estradiol, sex hormone–binding globulin, corticosteroid-binding globulin, and cortisol levels. Samples were obtained on 1 day during the tenth to twenty-first days of pill intake. All women received the respective oral contraceptive for at least 3 months. The test power was such that an 80% difference of 1 standard deviation of each target variable would have been detected ($\alpha = 0.05$; $\beta = 0.1$). No statistically significant differences were found in sex hormone–binding globulin, corticosteroid-binding globulin, or cortisol serum levels between both groups. Time and height of maximum ethinyl estradiol levels were identical as was the area under the curves. Ex vivo protein-binding analysis of the progestins revealed a free portion of 0.6% for gestodene and 2.5% for 3-ketodesogestrel as the active metabolite of desogestrel. Sex hormone–binding globulin–bound portions were much higher for gestodene (75.3% ± 9.1%) than for 3-ketodesogestrel (31.6% ± 12%). The remaining fractions were bound to albumin. In a second study, ethinyl estradiol-bioequivalence from pills A and B was investigated in 18 women in a controlled, single-dose, randomized, crossover design. The area under the ethinyl estradiol serum levels were identical up to 4 hours after pill intake between both treatments. According to the relatively low variation in data in this group of women, a 10% difference in ethinyl estradiol-availability could have been detected. Both studies indicate that the pharmacokinetics of ethinyl estradiol were independent of the concomitantly administered progestin, that is, desogestel and gestodene. (Am J Obstet Gynecol 1990;163:329-33.)

Key words: Gestodene, desogestrel, ethinyl estradiol, bioequivalence, sex hormone–binding globulin binding

Recently time-dependent changes in the serum levels of progestin have been reported in women who use either a combination oral contraceptive containing 75 μg of gestodene plus 30 μg of ethinyl estradiol (EE_2) (Femovan, pill A) or 150 μg of desogestel plus 30 μg of EE_2 (Marvelon, pill B). It was found that relative to 3-ketodesogestrel, higher total serum levels of gestodene were reached after repeated administration.[1-3] Results revealed a clear dependency of gestodene levels on concomitant changes in sex hormone–binding globulin (SHBG) serum levels. As an additional explanation, it was suggested that an "impeded metabolism" of gestodene could have contributed to the increase in serum levels. A similar interpretation has been offered for higher increases in serum EE_2, corticosteroid-binding globulin, and cortisol levels found after intake of pill A compared with those of pill B in the same comparative study.[4]

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Table I. Subjects characteristics and study design

Characteristics	*Study 1, group comparison*		*Study 2, intraindividual comparison*	
Preparation	F	M	F	M
(*n*)	(39)	(30)	(18)	(18)
Age (yr)	25 ± 5	24 ± 3	29 ± 5	
Weight (kg)	62 ± 10	59 ± 9	62 ± 7	
Height (cm)	170 ± 3	167 ± 3	170 ± 6	
Duration of treatment (mo)	11 ± 5	38 ± 24	Single dose	
Day of cycle	14 ± 3	14 ± 5	Changing	
Blood sampling times	1 Day between days 10 and 21 of cycle 0, 0.5, 1, 1.5, 2, 3, 4, and 24 hr after morning pill intake		0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hr after single pill intake	

F, Femovan; *M*, Marvelon.

Table II. Proportion (%) of free, SHBG-bound and albumin-bound gestodene and 3-ketodesogestrel in serum pools obtained from women using Femovan or Marvelon for at least 3 months

Progestin	*Gestodene*	*3-Ketodesogestrel*
Free fraction	0.6 ± 0.1	2.5 ± 0.2
SHBG bound	75.3 ± 9.1	31.6 ± 12.0
Albumin bound	24.1 ± 9.1	65.9 ± 11.9

Means ± SD.

The pharmacokinetics of sex steroids have been investigated extensively in the past.[5] Although various progestins show manifold differences in some important pharmacokinetic parameters, such as formation of active metabolite(s),[6] absolute bioavailability, terminal half-life of disposition from plasma,[7] and binding to carrier proteins,[8] their use in oral contraceptives was always defined by clinical experience and key studies on endocrinology. Furthermore, the daily pill intake schedule has never been adopted to pharmacokinetics.

The estrogen in most oral contraceptives, EE_2, is known for its large intersubject variability in pharmacokinetics.[9] Even oral bioavailability seems to vary to the same extent between subjects as within the same individual.[10] Therefore large groups of users are necessary to obtain a valid clinical response for small changes in EE_2 dose. In the past the EE_2 dose in combination oral contraceptives has been continuously lowered from 80 μg/day to 30 or even 20 μg/day to find an optimal balance between estrogen-dependent biochemical changes, efficacy, and bleeding control. Therefore the indication of increased serum EE_2 levels in pill A users[4] was assumed as the working hypothesis for two pharmacokinetic-clinical studies.

The aim of the first study was to investigate further the protein-binding characteristics of active ingredients, the serum levels of EE_2 and EE_2-dependent parameters, such as SHBG, corticosteroid-binding globulin, and cortisol, in two groups of women taking either pill A or pill B.

The aim of the second study was to check the EE_2 bioequivalence of both pills. The study has been performed in a controlled, single-dose, randomized, crossover design with a washout period of 1 week.

Material and methods

Subjects and trial designs. The details of subjects and studies are given in Table I.

Study 1 (group comparison) was an observational study in healthy women who used pill A or B for at least 3 months. The study was carried out at 5 locations (gynecologists) in Berlin and West Germany. After the purpose of the study was explained, the women were asked to donate blood immediately before and at specified times (Table I) after morning pill intake.

Study 2 was an open, single-dose, controlled, randomized crossover trial in 18 healthy women (Table I). The study protocol had been approved by an institutional review board and written informed consent was obtained. Between both treatments there was a washout period of 1 week.

Analysis. In study 1 all measurements were done in duplicate. Serum levels of EE_2 and gestodene were measured as previously described.[11, 12] SHBG, corticosteroid-binding globulin, and cortisol levels were determined by commercial kits (Diagnostic Products, Los Angeles, Calif., IRE Medgenix, Belgium, and H. Biermann GmbH, Federal Republic of Germany). Protein-binding experiments were carried out according to Hammond et al.[8]

EE_2 levels were analyzed in individual samples and serum pools representing time-averaged concentrations for the first 4 hours after pill intake. SHBG,

Table III. Mean values of pharmacokinetic parameters of EE_2 in two groups of women using Femovan or Marvelon

Pharmacokinetic parameters	*Femovan*	*Marvelon*
C_{max} (pg/ml)	106 ± 38	129 ± 51
MIN/MAX	38/212	37/235
t_{max} (hr)	1.8 ± 0.7	1.6 ± 0.7
MIN/MAX	0.5/4.0	0.5/4.0
$AUC_{0\text{-}4h}$ (pg · hr · ml^{-1})		
Direct	305 ± 115	354 ± 139
MIN/MAX	101/596	85/668
Pool (n = 38 / n = 29)	329 ± 123	374 ± 132
MIN/MAX	88/592	152/620
$AUC_{0\text{-}24h}$ (pg · hr · ml^{-1})	1246 ± 468	1360 ± 541
MIN/MAX	321/2226	349/2598

MIN/MAX, Minimum/maximum.

corticosteroid-binding globulin, and cortisol levels were also determined in these pools.

Analysis of samples from study 2 is ongoing. As the first results, serum levels of EE_2 in pooled samples are available in triplicate measures.

Statistical analysis. In study 1 groups were compared by an analysis of covariance with "day of cycle" and "duration of intake in months" as covariates. The null hypothesis was formulated as follows: mean values of all parameters are equal for both treatment groups.

The alternative hypothesis is that with given group size and a type 1 error of $\alpha = 0.05$ and a test power of $1 - \beta = 0.9$ a difference of $0.8\ \sigma = 80\%$ of 1 standard deviation) would be detectable with a t test.

The second study was evaluated by the Student t test for area under the curve (AUC)-EE_2 0 to 4 hours as a parameter for bioequivalence.

Results

Study 1. Protein binding of 3-ketodesogestrel and gestodene was analyzed in 28 and 37 serum pools, respectively. The results are given in Table II.

No specific binding was found for EE_2, and free fractions were identical under both treatments (1.7% ± 0.6% and 1.5% ± 0.2%).

Whereas 3-ketodesogestrel levels are not yet available, gestodene levels were characterized by AUC (0 to 4 hours) = 29.6 ± 10.4 ng · hr · ml^{-1} (n = 38).

Mean time courses of EE_2 levels in serum were similar in both treatment groups. Average pretreatment (0 hours) and 24 hours posttreatment levels between 26 and 28 pg/ml were nearly the same. Maximum EE_2 concentrations of 106 ± 38 pg/ml (gestodene group) and 129 ± 51 pg/ml (desogestrel group) were reached 1.8 and 1.6 hours after ingestion. No differences in AUC values – total (0 to 24 hours) and partial areas (AUC 0 to 4 hours) were found between both preparations (Table III).

Table IV. Serum levels of SHBG, corticosteroid-binding globulin, and cortisol in two groups of women using a low-dose combination (OC) containing either gestodene or desogestrel as the progestin

	Femovan	*Marvelon*
SHBG	n* = 38	n* = 27
nmol/L	186 ± 57	226 ± 64
MIN/MAX	92/299	94/363
CBG	n = 38	n = 38
μg/ml	89 ± 14	93 ± 14
MIN/MAX	57/121	64/122
Cortisol	n = 37	n = 27
ng/ml	281 ± 80	280 ± 62
MIN/MAX	145/461	173/387

CBG, Corticosteroid-binding globulin.

*Missing figures from two to three women in any parameter compared with Table III are because of the low sample volume left after EE_2 analysis.

AUC values (0 to 4 hours) as determined by single sample or pooled sample analysis were in complete agreement, demonstrating no necessity for pretreatment value subtraction. In every case pooled sample concentrations were clearly within the sensitive part of the standard curve of the assay. Under both preparations a wide range of SHBG levels was obtained (Table IV).

On average, 226 ± 64 nmol/L of SHBG was found for the desogestrel group and 186 ± 57 nmol/L for the gestodene group; the difference was not significant. Corticosteroid-binding globulin levels were almost identical numerically. Again, no statistically significant difference was found for cortisol serum levels measured under both preparations (Table IV).

Study 2. EE_2 levels in pooled serum samples were identical after ingestion of both OCs (Fig. 1). AUC (0 to 4 hours) after Femovan intake was 348 ± 65 pg · hr · ml^{-1} (range, 224 to 471) and 343 ±

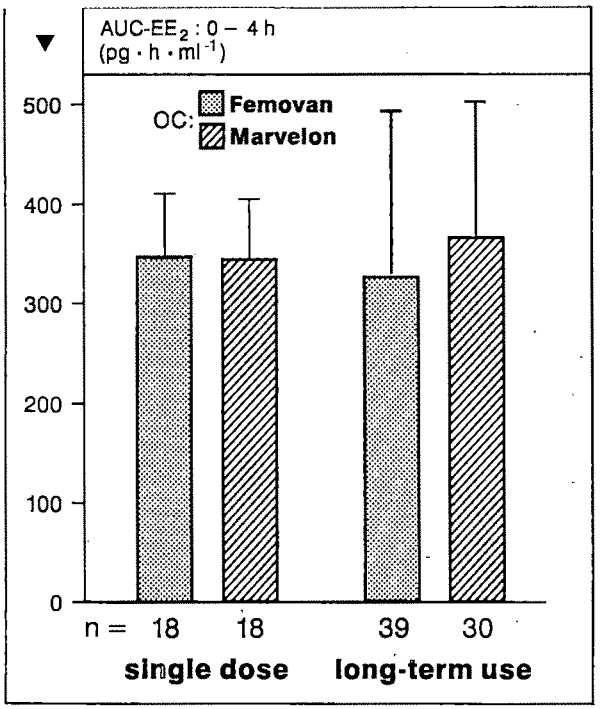


Fig. 1. Comparison of systemic availability of EE_2 between two low-dose combination OCs. The single-dose controlled, randomized, crossover study was conducted in 18 women, whereas the long-term study was conducted in two groups of 30 and 39 users, respectively. Means ± standard deviation of the area under the EE_2 curve up to 4 hours after pill intake are compared.

69 pg · hr · ml^{-1} (range, 222 to 462) after Marvelon treatment. Intrasubject variance of this parameter accounted for only about half of intersubject variance. According to the relatively low data variation, a 10% difference in EE_2 availability could have been detected.

Comment

Recently a new type of pharmacokinetic study has been published that compared actual progestin levels after repeated intake of two low-dose OCs containing different progestins (desogestrel and gestodene, respectively) at different dosages.[1-3] Active ingredients differ from each other by physicochemical properties (*n*-octanol/water partition coefficient is 285 for gestodene and 933 for 3-ketodesogestrel), absolute bioavailability, and metabolic clearance rate. Therefore, dose-corrected serum levels of equal height would not be expected. One very important property governing total serum progestin levels is protein binding, specifically, the extent to which a given progestin is bound to SHBG. In addition, the concentration of SHBG will markedly influence actual levels. The observation that steady-state levels of gestodene (daily dose, 75 μg) were four to five times higher than 3-ketodesogestrel levels (daily desogestrel dose, 150 μg) could be explained by the EE_2-dependent increase in SHBG during pill intake.[1,2] The present results confirm this explanation, showing that gestodene was highly (about 75%) bound to SHBG, whereas about 32% binding was found for 3-ketodesogestrel. Consequently, the free portion in serum was much lower for gestodene (0.6%) than for 3-ketodesogestrel (2.5%). According to the different protein-binding characteristics of gestodene and 3-ketodesogestrel, the free concentrations of both progestins are almost identical, although total serum levels differed about fourfold to fivefold.

The reason for higher increases in serum levels of gestodene compared with levels of 3-ketodesogestrel is the 10 times higher affinity to SHBG, which is reflected by the much higher proportion of specifically bound gestodene. Compared with 3-ketodesogestrel, gestodene is distributed differently in the body.

There is no need for additional (more speculative) explanations, such as "impeded metabolism," to interpret differences in actual progestin serum levels.

The present studies failed to confirm the observation of increased EE_2 serum levels with pill A compared with pill B.[4] Both trials were designed to detect statistically significant differences lower than those found previously, even at the first day of treatment.[4] This was the reason for our study 2, because in the single-dose bioequivalence study, an intraindividual comparison of EE_2 bioavailability could be accomplished. Interestingly, the data did not vary to the same extent as in study 1, and therefore an even 10% difference of mean EE_2-AUC values could have been detected between both preparations.

Therefore in conclusion the pharmacokinetics of EE_2 are independent of the coadministered progestins gestodene and desogestrel. Consequently, study 1 failed to show differences in the EE_2-dependent increase in corticosteroid-binding globulin and corticosteroid-binding globulin-dependent cortisol serum levels.

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ORAL CONTRACEPTIVES AND CARBOHYDRATE METABOLISM

Clinical aspects of the relationship between oral contraceptives, abnormalities in carbohydrate metabolism, and the development of cardiovascular disease

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Although large epidemiologic studies indicated no difference in the frequency of diabetes mellitus in nonusers and everusers of high-dose combination oral contraceptives, other studies had shown an increased risk of impaired glucose tolerance in current users, which is estimated to be roughly twice as frequent as that in nonusers. Women at risk of developing impaired glucose tolerance while receiving high-dose oral contraceptives either had previous gestational diabetes mellitus or were older, obese, or had a positive family history of diabetes mellitus. The tendency to decreased glucose tolerance seems essentially related to the dosage and chemical structure of the progestogen used in oral contraceptives, namely, estrane and particularly gonane progestins. However, increased frequency of impaired glucose tolerance and potentially diabetes mellitus are obviously not linked to the use of the more potent gonane progestins. The use of low-dose oral contraceptives, particularly with reduced progestogen content (such as in the triphasic formulations and last-generation monophasic preparations), is accompanied by a low risk of impaired glucose tolerance, even in previous gestational diabetes mellitus. The mechanism of decreased glucose tolerance in oral contraceptive users is unknown but seems related partially to increased peripheral resistance that is potentially caused by a postreceptor defect in insulin action. Changes in insulin production or metabolic clearance rate are not excluded by recent, sophisticated investigations of carbohydrate metabolism in oral contraceptive users. Impaired glucose tolerance and diabetes mellitus, chronic hyperglycemia, and hyperinsulinemia are believed to increase atherogenic risk either by their direct action or their effects on lipid metabolism. Newer epidemiologic studies now indicate that the incidence of cardiovascular disease in low-dose, low-risk, current oral contraceptive users has been substantially decreased. The use of low-dose oral contraceptives with reduced dosages of better adapted progestogens seems effective in decreasing alterations in carbohydrate metabolism and may thereby contribute to decrease further atherogenic risk in oral contraceptive users. (Am J Obstet Gynecol 1990;163:334-43.)

Key words: Glucose tolerance, insulin resistance, cardiovascular risk, oral contraception

Excess mortality and morbidity from cardiovascular disease (CVD) was observed in the 1970s mainly in women over 40 years of age, who had other established risk factors of CVD and who used combination oral contraceptives (OCs) containing high dosages of both estrogens and progestogens.[1] These events were related tentatively to increased atherogenicity and thrombogenic activity of OCs resulting from their steroid content. Accordingly, attempts directed at reducing the estrogen content of OCs were successful in decreasing thromboembolism,[2] and a further reduction of the progestogen content helped decrease vascular disease, mainly on the arterial side.[3] Moreover, Realini and Goldzieher,[4] in a reanalysis of these epidemiologic data, concluded that OC use may amplify well-known risk factors of CVD (such as cigarette smoking, hyperlipoproteinemia, hypertension, and diabetes) rather than be an independent risk factor alone.

Newer epidemiologic studies now indicate that current use of combined OCs with low dosages of both estrogen and progestogen by selected women at low risk for CVD is accompanied by a definitely low incidence of cardiovascular accidents. The latter now seems related more to coagulation disturbances than to enhanced atherogenesis.[5-7]

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Table I. Glucose tolerance in high-dose OC users

Type of studies	*No. of patients*	*Duration (mo)*	*No. of diabetics*
Oral and IV glucose tolerance tests in normal women receiving high-dose OCs	867 (22 studies)	1-48	34 (3.9%) (in 15/22 studies, no incidence of diabetes)
Glucocorticoid glucose tolerance in normal women receiving high-dose OCs	122 (4 studies)	1-17	61 (50%)
High-dose OCs in women with previous GDM	32 (4 studies)	0.5-6	14 (44%)

Data compiled from Kalkhoff RK. J Steroid Biochem 1975;6:949-56.
IV, Intravenous.

A reduction of the atherogenic risk by lowering the estrogen and more specifically the progestogen content of pills is probably partially achieved by reducing their adverse actions on lipoprotein and carbohydrate metabolism.[8]

Because diabetes mellitus (DM) is considered a primary risk factor for CVD[9] and because it has been known for more than 26 years[10] that OC use increases the risk of developing altered glucose tolerance, the purpose of this review is to outline some of the main data related to changing OC composition and its impact on carbohydrate metabolism in relation to the risk of CVD.

Effects of high-dose OCs (Table I)

In a large population of women taking high-dose OCs (50 to 150 μg of ethinyl estradiol [EE] and a high amount of progestogen), the 1-hour glucose tolerance-test (GTT) yielded serum glucose levels >11 mg/dl than those in non- or postusers, and the effect of the OC was added to the effects of age, obesity, and family history of diabetes. These changes were reversible on discontinuation of OCs.[11] Kalkhoff et al.[12] reported that irrespective of the length of OC intake, a relative incidence of impairment of glucose tolerance that approximated 20% developed in normal women using high-dose OCs.

A review of 22 studies of 867 women with normal glucose tolerance as assessed by an oral or intravenous GTT showed conversion to a diabetic-type test in 34 patients (3.9%) after 1 to 48 months of high-dose OC use. It is noteworthy that this increased frequency of abnormal glucose tolerance was observed in only 7 of the 22 studies. The existence of diabetogenic stress in users of high-dose OCs was further substantiated by investigations of glucocorticoid-sensitized GTTs, which yielded 50% abnormal responses, which corresponded to a 10- to 20-fold increase in the frequency expected in a general population.[12] These diabetic responses after prednisolone use were associated with subnormal plasma insulin responses during the first hour of the test as usually seen in patients with subclinical diabetes. However, return to a normal glucocorticoid-sensitized GTT was observed after 1 to 2 months of discontinuation of OC use.

Two other recent studies are worth reporting: in the Second National Health and Nutrition Examination Survey, impaired glucose tolerance (IGT) was observed in 13% of current high-dose OC users.[14] The second study reported 2-hour oral glucose tolerance test (OGTT) results from the Walnut Creek Contraceptive Drug Study, a 10-year prospective follow-up study. The 16% prevalence of IGT (including 2% of DM) was substantially higher than that of 8% in nonusers (including 1% of DM).[15]

In four studies reviewed by Kalkhoff[13] and totaling 32 women with previous gestational diabetes mellitus (GDM), a 2-week to 6-month duration of high-dose OC use was associated with a mean change of 44% in DM, a situation that is not always reversible on discontinuation of OCs. Moreover, in non-insulin-dependent DM, a deterioration in glucose tolerance was induced by high-dose OCs in 7 of 10 women, and in those suffering from insulin-dependent DM, the results were more variable, from minor changes in insulin requirements to extreme lability of insulin control.[13] In most of these cases, the response to OGTT or intravenous GTT was comparable as a whole: with high-dose OCs, a slight basal increase in fasting blood glucose and plasma insulin was observed, and after glucose loading, a lowered tolerance to glucose developed, eventually attained a pathologic level, and was associated with increased insulin response throughout the test or more markedly after 1 hour. Therefore the pill was considered to decrease insulin sensitivity and to represent a diabetogenic stress that preferably should not be administered to women with preexisting abnormalities in carbohydrate metabolism.

However, two important epidemiologic studies seemed more reassuring about the so-called diabetogenic effect of OCs. First, the survey of the Royal College of General Practitioners Study, which was in agreement with the Oxford FPA Study,[16] showed no difference in the frequency of DM incidence between high-dose OC current users (67,990 women-years), past users (42,663 women-years), and nonusers (111,252 women-years). They firmly concluded that "while it is still desirable to monitor OC users whose medical and family history indicate an increased likelihood of developing diabetes, the present results do not support

the belief that this contraceptive method increases the risk of DM."

Second, Duffy and Ray[17] reported a mean 8½-year follow-up study of 8652 women, which was made up of users, exusers, and nonusers of high-dose OCs. Screening for abnormalities in glucose metabolism revealed 118 cases of IGT or DM, with the same prevalence in carbohydrate abnormalities in all three categories of women. In particular, no permanent change in glucose status was observed as a result of OC use, and increased glucose intolerance was observed in women who were older, had a positive history of diabetes, or had a greater relative weight.

A preliminary conclusion from these sometimes divergent observations is that use of high-dose OCs is capable, probably in a predisposed population, of chronically increasing blood glucose and insulin levels and the incidence of IGT in the population, probably in a reversible manner. However, these long-term metabolic changes are of concern because they may facilitate atherosclerosis.[18]

Responsibility of the different steroid components of OCs in alterations in carbohydrate metabolism in users and impact on atherogenesis

As they relate to the estrogen compounds, ethinyl estradiol and mestranol, the studies of Spellacy et al.[19] showed that long-time use of these compounds did not significantly affect either blood glucose or plasma insulin after an OGTT. However, after 2 years of treatment with 80 μg of mestranol, the same group reported a small increase in serum glucose and insulin levels during an OGTT. In case of IGT, no further deterioration in glucose tolerance was observed with estrogen treatment.[20]

In contrast, numerous data, most of which were extensively reviewed by Spellacy[21] and Wynn,[22] indicate that progesterone, 17-acetoxyprogesterone derivatives, and 19-nortestosterone–derived progestins can, in an increasing order, increase both glucose and insulin levels after oral or intravenous administration of glucose, even if these drugs are given alone and in small dosages.

That not only the dose but the type of progestogen may be important is shown in several publications of Spellacy et al.,[21, 23] suggesting that megestrol acetate, a 17-acetoxyprogesterone derivative, would not affect glucose or insulin levels at a dose of 0.5 mg/day for 1 year, whereas 19-nortestosterone estrane derivatives, such as norethindrone or ethynodiol diacetate, would moderately and the gonane derivative norgestrel would markedly increase both blood glucose and plasma insulin levels.[21]

It is noteworthy that in the Walnut Creek Contraceptive Drug Study,[15] an analysis of glucose tolerance data by multiple linear regression analysis was undertaken to define dose-response relationships between the OCs and fasting, 1- and 2-hour glucose values: synthetic estrogens were not found to be related to measures of glucose tolerance, whereas examination of the regression coefficients indicated a 5 to 10 mg/dl increase in serum glucose for both 1- and 2-hour test results per milligram of structurally similar estrane progestins (norethindrone, norethindrone acetate, and ethynodiol diacetate). For the gonane progestin norgestrel, the slopes reflected an 18 of 35 to mg/dl increase/mg. One would expect that norgestrel-containing OCs would show the greatest decrease in glucose tolerance. However, because this compound or its active enantiomer levonorgestrel powerfully inhibits gonadotropins, it can be used in OCs in relatively lower amounts than estrane progestins, so that its impact on carbohydrate metabolism is finally brought to a comparable level.

In this respect, the prevalence of IGT and DM according to progestin exposure subgroups in the study of Perlman et al.[15] shows low values for the group taking a norgestrel-containing OC and is in fact slightly lower than that for other groups taking OCs containing estrane progestins.

Thus it must be remembered that not only nature and potency but also dose and type of administration must be considered, as well as adequately designed prospective studies conducted, for each estrogen-progestin formulation before any appreciation of its effect on glucose metabolism can be given accurately. If most of the impact on carbohydrate metabolism in OC users is related to the dose and potency of the progestin content, adaptation of low-dose OC formulation is mandatory in view of reducing carbohydrate alterations to a minimum, because chronic abnormalities can lead to increased cardiovascular morbidity and mortality. It is well known that DM is an independent risk factor of macrovascular disease, inducing a twofold to threefold increase in cerebral and coronary atherosclerosis and a sixfold to 20-fold increase in the arteriopathy of the lower limbs, with a substantial overall risk in young patients[24] and a particularly high incidence in women.[25]

IGT, as reflected by an increase in 2-hour blood glucose values, can be related to a twofold increase in cardiovascular death.[26, 27] Hyperinsulinemia, either in the fasting state or at 1 or 2 hours of an OGTT, has a role as a risk factor of CVD independent of other classic risk factors and at any level of blood glucose, with a twofold increase in the coronary disease mortality rate.[28-30] Chronic hyperinsulinemia may induce stimulation of vascular smooth muscle cell proliferation[31] and may cause alterations in lipoprotein metabolism by not only inducing the synthesis of very low–density lipoprotein triglycerides but also by decreasing high-density lipoprotein cholesterol and particularly the

Table II. Significant changes in carbohydrate metabolism associated with ≥6 months' use of low-dose combination OCs

Type of OC (μg/day) and investigations	*Length of study (mo)*	*Blood glucose level at end of study*	*Plasma insulin level at end of study*
Gonane progestogens			
EE 30 + LNG 150			
Ahren et al.[36]	12	No change	No change
Vandervange et al.[37]	6	No change	No change
WHO[38]	12	Increased	ND
Wynn[39]	36	Increased	Increased
Skouby et al.[40] (GDMs)	6	No change	Increased
EE 32 + LNG 92 (triphasic)			
Vermeulen et al.[41]	6	Increased	Increased
Luyckx et al.[43]	6	Increased	Decreased
Lepot et al.[42]	12	No change	No change
Skouby et al.[46] (partly GDMs)	6	No change	No change
Spellacy et al.[45]	12	No change	No change
Vandervange et al.[37]	6	No change	No change
EE 30 + DG 150			
Schijf et al.[48]	6	Increased	Increased
Luyckx et al.[43]	6	No change	Decreased
Jandrain et al. (unpublished)	12	Increased	Decreased
Vandervange et al.[37]	6	No change	No change
EE 20 + DG 150			
Fioretti et al.[49]	6	No change	No change
EE 30 + GTD 75			
Rabe et al.[50]	12	No change	No change*
EE 32 + GTD 79			
Lepot et al.[42]	12	No change	No change
Estrane Progestogens			
EE 35 + NE 1000			
WHO[38]	12	Increased	ND
EE 35 + NE 750 (triphasic)			
Rabe et al.[55]	12	No change	No change
Spellacy et al.[45]	12	No change	No change
EE 35 + NE 500			
Spellacy et al.[51]	12	No change	No change
EE 35 + NE 400			
Spellacy et al.[52]	12	No change	No change
Pregnane progestogens			
EE 35 + CA 2000			
Jandrain et al. (unpublished)	12	Increased	No change

EE, Ethinyl estradiol; *LNG,* levonorgestrel; *DG,* desogestrel; *GTD, gestodene; NE,* norethindrone; *CA,* cyproterone acetate; *ND,* not determined; *GDM,* previous gestational diabetes; *WHO,* World Health Organization.

*Ongoing study, statistical analysis not definitive.

HDL_2 cholesterol subfraction (the so-called cardioprotective fraction), as shown in noninsulin-dependent DM.[32, 33] Although still somewhat controversial,[34] these observations may be relevant to the increased risk of atherogenesis in cases of hyperinsulinemia.

Certainly in that regard, the new OCs with overall reduced levels of estrogen and progestin, with particular emphasis on reducing the most potent progestins such as levonorgestrel and other gonanes, should be suited better to exerting only a minor impact on carbohydrate metabolism and thereby partly on potential atherogenicity. Moreover, because abnormalities in glucose metabolism may be observed in OC users, particularly, if additional risk factors such as obesity, family history of diabetes, age, or antecedent of GDM are present, it is essential to evaluate how to minimize the risk in OC users by proper patient selection.[21]

Effects of low-dose OCs (Table II)

As the first "sub fifty" pills containing lower levels of EE combined with low doses of progestins were introduced in the mid-1970s and became widely used only in the 1980s, epidemiologic data with a sufficiently long follow-up period are very scarce.

A large prospective study on diabetic risks was initiated in 1985 in the greater Paris area (Telecom Study) by Eschwege et al.[35] with 1112 healthy women of reproductive age participating. They were analyzed on a cross-sectional basis according to their use of oral contraception: 369 women (30%) were current OC users, and among them 79% used low-dose pills. After adjustment for age, weight, and risk factors for diabetes, those taking the pill had significantly higher fasting serum insulin, triglycerides, and 2-hour 75 gm OGTT blood glucose levels compared with those who did not.

In this restricted series no difference was seen between users of high- and low-dose OCs.

These authors concluded that the insulin-resistance markers, which have recently been cited as risk factors of ischemic vascular disease, should still be carefully monitored in pill users.

Most of the studies on which we rely for analysis of carbohydrate metabolism during use of low-dose OCs have restricted numbers of women, usually 10 to 20, highly selected for exclusion of vascular risk factors, and usually subjected for 6 to 12 months (rarely more) to OGTTs in order to monitor mainly changes in blood glucose and plasma insulin and eventually circulating levels of pyruvate, glucagon, C-peptide, and glycosylated hemoglobin A_1C, as well as monocyte or erythrocyte insulin receptors. Thus we must rely more on biochemical than epidemiologic data to appreciate the potential of these drugs to alter glucose metabolism. On the contrary, well-designed biologic studies can also shed new insight into the mechanism of action of contraceptive steroids on carbohydrate metabolism and potentially unrecognized metabolic alterations.

Low-dose OCs containing levonorgestrel

The effects on carbohydrate metabolism of the combination preparations containing an intermediate dose of levonorgestrel, 150 μg/day, are controversial. Ahren et al.[36] did not observe any increase in blood glucose, and plasma insulin levels when EE 30 μg + levonorgestrel 150 μg was used for 12 months either in an oral formulation or as a vaginal ring.

Vandervange et al.[37] subjected 10 healthy women to the same combination OC and did not observe statistically significant changes in plasma glucose and insulin levels and areas under the curves when OGTTs were compared before and at 6 months.

The World Health Organization multicenter trial[38] compared two low-dose combination OCs—EE, 35 μg, with norethindrone, 1 mg, and EE, 30 μg, with levonorgestrel, 150 μg, for 12 months in 847 users. In both pill groups, an increase in 2-hour glucose was observed at both 3 and 12 months without any significant difference between groups. Eight percent of OC users had IGT compared with 4% in an intrauterine device control group (n = 195). However, at 12 months, one third of OC users with IGT detected after 3 months had returned to normal glucose tolerance.

Wynn[39] observed a deterioration in glucose tolerance that increased with time for up to 36 months of study when the same OC containing EE 35 μg + levonorgestrel 150 μg was used. An accompanying increase in insulin response developed during OC use, but this increase could not prevent an increase in the ratio of incremental glucose area: incremental insulin area. IGT developed in six women, three of whom had overt DM after 3, 12, and 30 months, respectively. However, the major drawback of this study is an uncommonly high drop-out rate: 210 women entered the study and only 17 remained in the study after 3 years, which, of course, does not allow for epidemiologic conclusions to be drawn. It is noteworthy that in a small group of 10 women with previous GDM using the same EE 35 μg + levonorgestrel, 150 μg preparation for 6 months, IGT was not observed, but a significant rise in plasma insulin values was seen.[40] Because of these controversial results, it was interesting to analyze the results obtained when the influence of the triphasic formulation containing EE and levonorgestrel was studied, since this preparation contained only a mean daily dose of 92 μg of levonorgestrel, a substantial decrease of 39% compared with the monophasic "low-dose" preparation. In one preliminary study, blood glucose and plasma insulin levels increased after 6 months, but these changes were not considered clinically relevant.[41]

In a careful 12-month prospective study,[42] we compared 24 treated subjects at 0, 6, and 12 months of use with a group of matched nonusers. No change in glucose tolerance was recorded in any individual during treatment, and a moderate but statistically significant increase in plasma insulin response was only transiently observed during the sixth month of study. In addition, no changes in the number of and affinity of insulin erythrocyte receptors were recorded. These results were at odds with a previous 6-month study,[43] in which we observed a slight decrease in glucose tolerance that was associated with a decrease in insulin response when compared with pretreatment levels. However, this difference may also be related to circannual changes in glucose-insulin homeostasis as previously observed by Reinberg et al.[44] The protocol of our subsequent study was modified accordingly to avoid this physiologic interference. In a study of 10 women receiving this triphasic combination for 6 months, Vandervange et al.[37] were unable to observe any alteration in carbohydrate metabolism except for a slight but significant increase in blood glucose at 30 minutes of the OGTT at 6 months of use. Very recently Spellacy et al.[45] reported that OGTTs performed on 28 women before and after 12 months of using this levonorgestrel triphasic OC showed no significant changes in glucose or insulin. Moreover, a study conducted with this levonorgestrel triphasic OC for 6 months in normal women and those with previous GDM did not show significant changes in blood glucose, or plasma insulin, and glucagon response to oral glucose at 2 and 6 months despite higher blood glucose levels before entering the study in women with previous GDM.[46]

These same authors analyzed under the same clinical circumstances the variation in insulin sensitivity in women during a 6-month period of levonorgestrel

triphasic OC treatment using the hyperinsulinemic-euglycemic clamp technique.[47] They observed that use of this OC decreased slightly, but not significantly, insulin sensitivity in healthy women. In previous GDM the decrease was slightly more pronounced and reached significance, but this decrease was not sufficient to alter glucose tolerance.[47] From these numerous studies devoted to OCs containing either intermediate (150 μg) or low (92 μg, mean daily dose) dosages of levonorgestrel and considering the number of women studied, including high-risk groups (GDM), the length of the studies, and the accuracy of the methodologies (use of control groups, sophisticated investigation such as the clamp technique), it seems that a drastic reduction in the dose of this potent gonane progestin is associated with a substantial reduction or even a lack of adverse effects on carbohydrate metabolism. A minor influence on IGT that developed in nondiabetic women cannot be discarded—as for other low-dose OCs such as EE, 35 μg, and norethindrone, 1000 μg—during use of EE, 35 μg, and levonorgestrel, 150 μg, formulations.

Low-dose OCs containing desogestrel

Although preliminary data[48] indicate that after 6 months of use with monophasic EE, 30 μg, with desogestrel, 150 μg, significant increases in blood glucose and insulin levels were recorded, our study[43] did not reveal any change in glucose tolerance but detected a slight decrease in insulin response during the OGTT performed at 6 months of OC use. At that time it was felt that circannual changes could partly account for this observation. However, in a recent prospective study of 21 women taking this monophasic OC for 12 months, we observed a slight borderline increase in blood glucose levels (without any trend to IGT) and again a decrease in insulin response compared with pretreatment and 6-month responses, whereas C-peptide was significantly increased. This could be related to a somewhat increased rate of metabolic clearance of insulin with use of this drug, but this necessitates more detailed studies (Jandrain B, Humblet D, Jaminet C, Scheen AJ, Gaspard U, Lefebvre PJ. Unpublished data). In the study by Vandervange et al.[37] no change in glucose and insulin response and hemoglobin A_{1c} and glycosylated proteins could be observed after 6 months of use with this monophasic OC. Moreover, using the recently introduced monophasic formulation EE, 20 μg, and desogestrel, 150 μg, no alteration in fasting insulin and glucose levels was seen after 6 months of use with this OC, and the response to OGTT was also unchanged.[49]

Low-dose OCs containing gestodene

This gonane progestin recently introduced in monophasic OCs (EE, 30 μg, and gestodene, 75 μg) or in a triphasic formulation (EE, 32 μg, and gestodene, 79 μg, mean daily dosage) is interesting because of its potent gonadotropin-inhibiting effect, which allows it to be used in very low dosages in OCs.

Preliminary results of the study of Rabe et al.[50] performed on 28 women during 12 months using the monophasic formulation showed a slight increase in glucose and insulin levels during OGTTs, with no subject developing IGT. Our results with the gestodene triphasic formulation are particularly encouraging, because they show[42] in the 20 women using this OC for 12 months that glucose tolerance and insulin response during OGTTs are unchanged. This gestodene triphasic OC behaved even better than the levonorgestrel triphasic OC with which it was prospectively compared.

Low-dose OCs containing norethindrone

We reported the results of the World Health Organization Study on the monophasic formulation EE, 35 μg, and norethindrone, 1000 μg, which showed increased blood glucose levels at 3 and 12 months of use, and was associated with a slight increase in the incidence of women with IGT during treatment.[38] No change in carbohydrate metabolism was apparently observed with low-dose combination OCs containing either 500 or 400 μg of norethindrone.[51, 52] However, it must be remembered that 1 year of use of progestogen-only pills containing 350 μg of norethindrone or 250 μg of ethynodiol diacetate, another estrane progestin, enhanced blood glucose and plasma insulin concentrations despite the small dosage of these "less potent" (versus gonane progestins) steroid compounds.[53, 54] In the study of Rabe et al.,[55] the triphasic preparation containing EE, 35 μg + norethindrone, 750 μg, caused a transient increase in 1- and 2-hour blood glucose values and plasma insulin levels. At 12 months, however, the differences in glucose tolerance and insulin response were no longer statistically significant and no case of progression to IGT was recorded. The lack of effect on glucose tolerance with this OC was also recently reported by Spellacy et al.[45] in 33 women after 1 year of use.

Low-dose OCs containing cyproterone acetate

Cyproterone acetate is a pregnane progestin with antiandrogenic and antigonadotropic activities, usually used in high dosages for the treatment of hirsutism and other clinical conditions.[56] As discussed earlier, 17-acetoxyprogesterone–derived progestins have less metabolic impact than nortestosterone-derived progestins.[13] Indeed, an interesting study of Seed et al.[57] with sequential use of EE and cyproterone acetate at high dosages (10 to 20 times that used in OCs) showed decreased glucose tolerance and increased insulin levels in treated women. It did not, however, clearly ascertain whether increased insulin response was related to in-

creased pancreatic output, because C-peptide levels were not uniformly increased. In a recent still unpublished study (Jandrain B, Humblet D, Jaminet C, Scheen AJ, Gaspard U, Lefebvre PJ), we showed in 19 healthy women using a low-dose combination of EE, 35 μg, with cyproterone acetate, 2 μg, a slight decrease in glucose tolerance at 12 months of use and an associated modest increase in insulin and C-peptide responses during OGTTs, probably related to a slightly decreased insulin sensitivity. No case of progression to IGT was observed in this study. These results are well in agreement with the fact that pregnane compounds have only a limited impact on carbohydrate metabolism; a clearcut difference with the effects of low-dose combined OCs containing 19-nortestosterone–derived progestins is not observed despite low or even antiandrogenic properties of the former compounds. It should be remembered, however, that natural progesterone itself is not devoid of some effect on glucose metabolism.[22]

Comment

Recent epidemiologic studies[58] indicate that selection of women with low levels of recognized risk factors for CVD, such as smoking, hyperlipoproteinemia and hypertension, and the use of low-dose OCs (i.e., low estrogen doses combined with low progestogen dosages) are associated with a particularly low incidence of CVD. In fact low-dose OCs are considered amplifiers of risk factors and not primary risk factors by themselves.[4] Excess mortality or morbidity caused by CVD is restricted to current users of low-dose OCs only and are probably related to persistent excess of thrombogenic rather than atherogenic activity of these low-dose OCs.[58] The atherogenic risk of high-dose OCs is partly attributable to their adverse effects on lipid and carbohydrate metabolism.[59] As it relates to carbohydrate metabolism, it is now well established that DM, and very probably chronic hyperglycemia and hyperinsulinemia, can be considered risk factors of atherosclerosis.[18] Progestins contained in OCs, most of which are derived from 19-nortestosterone, have the potential to decrease glucose tolerance and increase insulin resistance by mechanisms still largely unknown. In some studies the use of standard dose OCs containing high levels of these progestins has been associated not only with biochemical alterations in the carbohydrate metabolism previously described but also with a trend to increasing the incidence of IGT and even progression to overt DM, which is sometimes not reversible, despite discontinuation of the OCs.[13]

However, large epidemiologic studies[16, 17] could not substantiate with long-term follow-up of large populations of women taking high-dose OCs any trend to increased incidence of DM or even IGT. In fact this incidence was increased in older women with obesity, a positive family history of DM, or previous GDM, and not specifically in relation to OC use. Notwithstanding this reassuring observation, it remains that high-dose OCs can chronically increase blood glucose and plasma insulin levels and may contribute to atherogenesis and excess CVD, as observed in earlier epidemiologic studies.[1] The progestin part of the OCs is mainly responsible for alteration in carbohydrate metabolism,[21] and among progestogens, 19-nortestosterone derivatives have more impact than 17-acetoxyprogesterone derivatives. Within 19-nor progestins, the more potent gonane derivatives, such as norgestrel, provoke more changes in carbohydrate metabolism than do estrane compounds.

However, the potential of norgestrel to increase the incidence of IGT and DM has not been demonstrated[15] inasmuch as the dose of this progestin can be safely reduced in OCs because of its potent antigonadotropic activity; this reduction is instrumental in decreasing the effect of norgestrel on carbohydrate metabolism.

A large number of studies, many of which are summarized in Table II, have been devoted to the impact of low-dose monophasic and triphasic OCs, all of which are characterized by low levels of estrane, gonane, or pregnane progestogens.

Most of these prospective studies have used repeated, standardized, oral glucose loads to assess before and at 3 to 12 months of use (rarely longer) the effect of low-dose OCs on carbohydrate metabolism. Most point to only slight decreases in glucose tolerance (usually mean areas under glucose curves + 10% to 15% compared with pretreatment values) with very rare cases of progression to IGT, if any. Usually a mild increase in insulin response to glucose is observed (mean areas under insulin curves + 10% to 30%) and is often interpreted as a reflection of increased insulin resistance, potentially at the postreceptor level.

Decreased insulin sensitivity is supported by analysis of the hyperinsulinemic-euglycemic glucose clamp technique[47] in users of low-dose levonorgestrel triphasic OCs. In a few studies, monocyte or erythrocyte insulin receptor number and affinity have been analyzed in relation to pill use, and the absence of change[42, 43] or slight changes[60] were observed, with no relation to changes in glucose tolerance. Glucagon basal levels or suppressibility during OGTTs was mainly unchanged or decreased in cases of OC intake in which insulin response to OGTT was not increased, such as during use of the monophasic low-dose EE + desogestrel, or enhanced in cases in which insulin response to OGTT was also increased, such as during use of the triphasic EE + levonorgestrel or the monophasic EE + cyproterone acetate.[42, 43] Despite some discrepancies in the results obtained, most of these metabolic studies

point to a low potential for low-dose pills to alter carbohydrate metabolism. Most changes observed are not even statistically significant, and when they are, the clinical relevance of these small differences can be questioned. Moreover, because of the low dosages of progestogens used in the new OCs, no study seems able to show a difference between pills containing <1 mg of norethindrone, <150 μg of levonorgestrel, or containing low dosages of desogestrel and gestodene, as far as carbohydrate metabolism is concerned.

However, many of these studies show a number of worrisome shortcomings that reduce considerably the interest and potential meaning of the results. First, and this is in agreement with the assertions of Crook et al.,[61] prospective studies of carbohydrate metabolism should be directed to clinically well-characterized homogeneous populations of women, with a sufficient number of subjects (probably 20 or more in relation to the methodology used) and for a sufficient duration of time (probably 12 months or more). The design of the studies should be more standardized, and circannual rhythms of glucose metabolism must be taken into account.[34]

The use of glucose challenge tests has been fruitful despite their well-known shortcomings. However, they should usually be better standardized, and the data related to blood glucose and plasma insulin levels generated in the studies should be more carefully analyzed and described.

This would at least help to more easily compare these studies. New large-scale epidemiologic studies, such the recent and incipient Telecom Study,[35] are needed to better ascertain whether low-dose pills are associated with a continuing low vascular risk.

Moreover, it is mandatory to understand better the mechanism underlying decreased tolerance to glucose in pill users by indepth studies of pancreatic B-cell function, insulin release, and kinetics during OC use. In particular, regular assessment of C-peptide levels should be part of these studies. The use of the euglycemic clamp technique at different insulin levels, analysis of tracer kinetics, and indirect calorimetry should help to better characterize insulin sensitivity. Alternatively, the use of the recently described minimal modeling method[62] could be very helpful to assess insulin sensitivity and B-cell function during OC use. In addition, studies of insulin receptor properties and postreceptor intracellular events should be envisaged.

Indepth study of the effects of different progestogens contained in OCs could well uncover different mechanisms of action more specific of a given steroid. For instance, such a progestogen might particularly alter postreceptor intracellular metabolism of glucose, whereas another progestin may more specifically alter the metabolic clearance rate of insulin. Uncovering such mechanisms may help develop progestins that potentially are more adapted to their contraceptive function, with a lesser impact on carbohydrate metabolism, because chronic hyperglycemia and hyperinsulinemia, even of a moderate nature, are best to be avoided as far as CVD is concerned.[18]

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Mechanism of action of oral contraceptives on carbohydrate metabolism at the cellular level

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Although the available scientific data on the undesired metabolic effects of sex steroids have accumulated rapidly, most are of a descriptive nature, and only a few studies elucidate the impact at the cellular level and the possible interrelationship between different metabolic systems. This review summarizes the influence of different contraceptive steroid combinations on glucose metabolism and points to the possible mechanisms behind a disturbance of the euglycemic homeostasis with a concomitant change in lipid metabolism. Today the general concept is that the influence of combined sex steroid products on glucose metabolism is mainly caused by the progestogen components, although artificial estrogens may act synergistically. The diabetogenic effects of the progestogens make it important to consider the development during the last decade of the new more selective progestogens of the gonane type. From recent studies it seems, however, that intake of contraceptive combinations of ethinyl estradiol in combination with these types of gonanes, such as desogestrel and gestodene, may also be accompanied by increased insulin resistance, specifically, a hyperinsulinemic response to a glucose challenge despite unchanged glucose values compared with a baseline test. This is similar to observations made with combinations of ethinyl estradiol and other more traditional types of progestogens of the gonane and estrane type. It is conceivable that the diabetogenic effects of the progestogens are caused by a change in insulin receptor binding or a postreceptor defect in the cellular insulin action. The clinical implications of the diabetogenic effects of the sex steroids are hard to interpret, but more long-term exposure of arterial tissue to elevated concentrations of glucose and insulin results in inhibition of lipolysis and synthesis of cholesterol and triglycerides, which result in the development of lipid-filled lesions—fatty streaks—similar to those of early atherosclerosis. (AM J OBSTET GYNECOL 1990;163:343-8.)

Key words: Oral contraceptives, glucose metabolism, insulin resistance, lipogenesis

The use of estrogens and progestogens in oral contraceptives has caused increased awareness of the effects of gonadal steroids on metabolic processes and especially on the glucose and lipid metabolism. One of the earliest metabolic effects observed was the risk of developing reduced glucose tolerance.[1, 2] It has been suggested that the women at greatest risk are those with episodes of impaired glucose tolerance, for example, during pregnancy, or those with a strong family history of diabetes.[3] However, major epidemiologic studies indicate that oral contraceptive users have more than doubled the risk of developing a deterioration in glucose tolerance compared with nonusers.[4, 5] In contrast, normal women have a very limited, if any, risk of developing clinically frank diabetes during oral contraceptive treatment.[6] During the last decades, many studies have attempted to quantify the impact of oral contraceptives on glucose metabolism, because the first

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reported changes in carbohydrate metabolism were based on small metabolic studies and because the potential diabetogenic effects remain a concern to public health due to the enormous number of pill users. However, the discrete effects of sex steroids on glucose metabolism make it mandatory to ensure monitoring of the possible changes with precise and accurate measurements. The study period should not be too short, that is, at least 6 months, and the number of women included in the study sufficiently high to enable detection of the expected changes. Moreover, when studying changes in glucose metabolism, possible confounding factors exist, such as differences in nutritional habits, in addition to ethnic and circannual variations in the endogenous maintenance of glucose homeostasis. For obvious reasons not all clinical studies on the metabolic effects of oral contraceptives have been performed under ideal circumstances, but aside from methodologic problems that may be difficult to circumvent, most studies are also confined by their descriptive nature. Only a few elucidate the mechanism of action at the cellular level and the possible interrelationship between the glucose and lipid metabolic systems. This review summarizes the influence on glucose metabolism of different contraceptive steroid combinations, the possible mechanism behind a disturbance of the euglycemic state, and the concomitant impact on lipid metabolism.

Influence on glucose metabolism of high- and low-dose preparations

Early studies on the metabolic effects of oral contraceptives demonstrated consistent impairment of glucose tolerance by increases in fasting glucose and insulin levels and in the response of these variables after a glucose challenge.[1, 2, 7] Studies by Spellacy et al.[8-11] also revealed that the artificial estrogenic components used in combined oral contraceptives have little or no deteriorating influence on glucose homeostasis when administered alone, whereas progestogens, to a certain extent, were able to mimic the diabetogenic effect of the combined compounds. Since these inventive studies were published, a bulk of scientific data has become available on the undesired metabolic effects of sex steroids, but much confusion still exists on the results and their clinical interpretation. One of the reasons for the discrepancy between data from different studies is failure to discriminate between qualitative and quantitative differences between the various combined oral contraceptive compounds with identical contraceptive effect. First and foremost, a distinction should be made between preparations containing 50 μg or more of ethinyl estradiol and high progestogen content and the newer low-dose preparations with 35 μg or less of estrogen and reduced amounts of progestogen, because the impact on glucose metabolism is clearly shown to be dose dependent.[3] In addition, differences in the biochemical structure of the steroid components should be considered because the molecular configuration decides both the receptor-mediated and the direct cellular effects. In contrast to the artificial estrogens used in oral contraceptives, ethinyl and mestranol, the progestogens are represented by a variety of steroid formulations, with marked differences in their pharmacodynamic responses and classified estranes, gonanes, and pregnanes. The estrane progestogens include norethindrone acetate, lynestrenol, norethynodrel, and ethynodiol diacetate, and all these compounds must be transformed metabolically into norethindrone to become biologically active. For many years the gonanes have been represented in oral contraceptives only by norgestrel and its active component, the dextroisomer levonorgestrel, but in recent years new types of progestogens of the gonane type, such a desogestrel, gestodene, and norgestimate, have succeeded the widely used norgestrel/levonorgestrel in the combined type of oral contraceptives. Pregnanes include megestrol, chlormadione acetate, and cyproterone acetate. As opposed to estranes and gonanes, which in structure are related to the reduced form of testosterone, 19-norethindrone, the pregnanes are derivatives of 17-hydroxyprogesterone, but today cyproterone acetate, which has specific antiandrogen properties, is the only pregnane used in oral contraceptives. Thus as a consequence of the variety of progestogens, it is useful to distinguish between the categories when considering the metabolic effects. The introduction of the new generation of gonanes has, however, also made it necessary to differentiate within these types of progestogens because despite structural similarities they display differences in biologic properties.[12]

Today two important questions are, do low-dose preparations have any deleterious effects of clinical significance on glucose metabolism and are there differences in the metabolic effects between compounds depending on the type of progestogen used? Wynn and Godsland[13] reported that the incidence of impaired glucose increased steadily from 5% to 30% during treatment with low-dose monophasic ethinyl estradiol plus levonorgestrel for 36 months and significantly less influence on glucose metabolism from compounds containing norethindrone. Not all investigators[14, 15] substantiated these findings. Using a monophasic preparation of 30 μg of ethinyl estradiol and 150 μg of levonorgestrel, we found no changes in fasting glucose, insulin, or glucagon values after 2 and 6 months in healthy nondiabetic women. After hormonal intake for 6 months, the insulin response to oral glucose increased significantly, but no change was observed in glucose tolerance.[16] The introduction of triphasic ethinyl estradiol—levonorgestrel preparations was part of the strategy to reduce the metabolic side effects by reduction of the steroid dose. We examined the effect of such

a preparation in normal women and in women with previous gestational diabetes. In both groups the triphasic preparation resulted in a significantly lower insulin response to oral glucose.[17] The new "selective" progestogens of the gonane type, desogestrel and gestodene, with a high affinity for human progesterone receptors, have only been marketed for a limited period, but it appears from present investigations with both monophasic and triphasic combinations that they may have a similar effect on glucose metabolism as the monophasic ethinyl estradiol—levonorgestrel combinations, that is, a hyperinsulinemic response to oral glucose.[18] Also, intake of low-dose combined monophasic preparations containing the pregnane progestogen cyproterone acetate may result in an increased area under the insulin curve during the oral glucose tolerance test.[19] To summarize, there seems to be no risk of impairment of glucose tolerance during short-term intake of combined low-dose oral contraceptives in young normal women, but during intake of almost all preparations marketed, there have been reports of a hyperinsulinemic response to oral glucose. The short-term effects of mild hyperinsulinemia are hardly of clinical relevance, although the observation should not be ignored. Among the changes associated with aging is a decline in glucose tolerance preceded by hyperinsulinemia.[20] Thus long-term use of oral contraceptives or expanded use by women also >35 years old may modulate the physiologic change in glucose tolerance and thereby facilitate the occurrence of coronary heart disease.[21] This potential association makes it mandatory with investigations on the possible sustained effect on insulin secretion and insulin action in users of oral contraceptives.

Mechanisms of action

In nearly all investigations on the influence of oral contraceptives on glucose metabolism, the traditional glucose tolerance test has been used either intravenously or orally. Although such measurements of plasma glucose combined with simultaneous measurements of plasma insulin and eventually glucagon levels are necessary and useful when glucose intolerance is described and classified, they give insufficient information on the mechanism that underlies the disturbances in the glucose homeostasis during hormonal treatment. However, the common observation in pill users of a hyperinsulinemic response to a glucose challenge indicates a change in the important biologic balance between insulin secretion and insulin action. Pancreative hyperresponsivity is the physiologic response to impaired insulin tissue action to keep glucose tolerance normal. Therefore decrease in insulin sensitivity at the cellular level in peripheral tissues is the most obvious explanation for the influence of oral contraceptives on glucose metabolism although a change in the metabolic clearance rate of insulin in the liver may also play a role. Insulin initiates cellular action by binding to a specific glycoprotein receptor on the surface of the cell. The first direct demonstration of insulin receptors was performed more than 15 years ago, and further experiments established the relationship between the binding reaction and the subsequent changes in intracellular metabolic pathways.[22] The receptor is a tyrosine-specific protein kinase with two subunits. The α subunit binds to insulin, which causes an autophosphorylation of the tyrosine molecule of the β unit. This results in a stimulation of glucose transport across the cell membrane.

Insulin receptors and oral contraceptives. Several studies have been performed on insulin receptor binding during intake of oral contraceptives. Nearly all studies are in vitro measurements on circulating cells, first and foremost erythrocytes and mononuclear leukocytes. Most often Scatchard analyses have been applied to quantitate insulin-binding capacity and affinity. Using this technique Tsibris et al.[23] and De Pirro et al.[24] found after administraiton of monophasic compounds (ethinyl estradiol, 50 μg or 30 μg, plus 250 μg of norgestrel or 150 μg of levonorgestrel and 50 μg or 30 μg of ethinyl estradiol plus 500, 1000, or 400 μg of norethisterone) cessation of the physiologic variation of insulin receptor concentration and affinity reported earlier in the menstrual cycle. No differences in binding parameters were found between the luteal phase in the control cycle and the measurements performed during hormonal intake. We measured the influence of the triphasic ethinyl estradiol–levonorgestrel compound on insulin receptor binding to monocytes and erythrocytes in nondiabetic women and in women with previous gestational diabetes[25] to see whether the encouraging clinical results previously obtained with the same contraceptive compound[17] could be substantiated by estimations of the insulin antagonistic effects at receptor levels.

Before hormonal treatment, the women with previous gestational diabetes had significantly impaired glucose tolerance when compared with healthy control subjects, but no differences in insulin receptor binding were observed. Glucose tolerance and the insulin response to oral glucose remained unchanged in both groups during the treatment period. In control subjects a significant decrease in insulin receptor binding to monocytes was observed after hormonal intake for 6 months, whereas insulin receptor binding remained unchanged in women with previous gestational diabetes. No correlation was found between glucose tolerance and insulin receptor binding to erythrocytes and monocytes during intake of low-dose oral contraceptives.

However, studies of insulin binding to receptors on monocytes and erythrocytes are not always easily in-

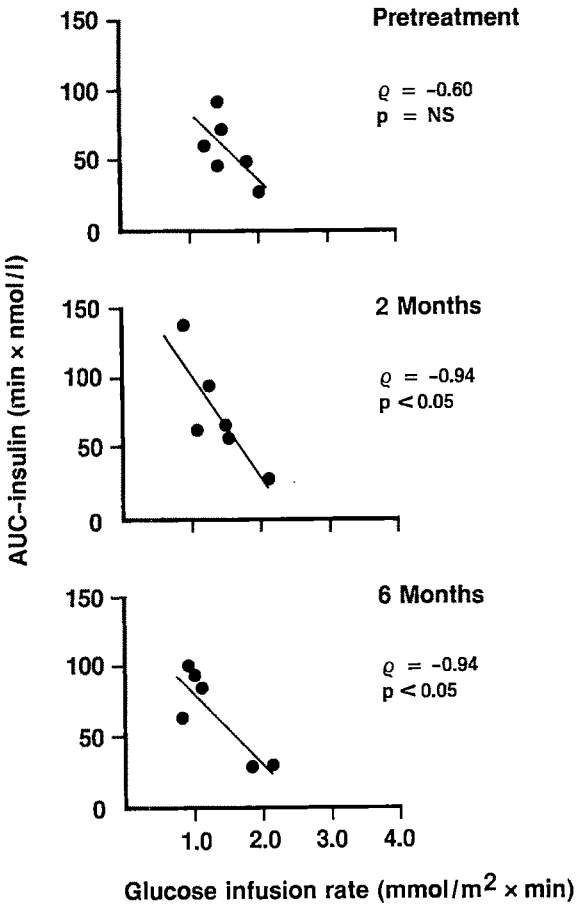


Fig. 1. Correlation between area under insulin curves *(AUC)* and glucose infusion rates during euglycemic clamp investigations in normal women ($N = 7$) receiving a low-dose oral contraceptive (ethinyl estradiol plus levonorgestrel) for 6 months.

terpretable, partly because of methodologic problems and partly because of lack of clear evidence that changes in insulin binding blood cells in humans are comparable with "true" changes in insulin-responsive tissues. Lack of correlation between measurements in erythrocytes and monocytes has been previously reported, although results from correlation studies vary. The discrepancies may be explained by the fact that erythrocytes have a highly specialized membrane that is unable to synthesize new insulin receptors and thus lack the capacity to replace insulin receptors lost during aging of the cells.

In vivo clamp investigations and oral contraceptives. Because measurements of insulin binding to blood cells in vitro do not necessarily reflect insulin receptor function in vivo and give no information on postreceptor defects, various other methods have been invented to assess insulin sensitivity. The euglycemic clamp technique[26] is one of the best because it surmounts the effect of changes in blood glucose concentration on glucose utilization. With this technique plasma insulin concentration is increased to a constant level by a primed, continuous intravenous insulin infusion. Plasma glucose is maintained at the euglycemic level by means of variable glucose infusion. After the initial insulin infusion, a quasi steady state is reached in which total glucose turnover can either be quantified by means of a (^{3}H)3-glucose infusion or calculated from the unlabeled exogenous glucose infusion by a nonequilibrium equation, provided endogenous (hepatic) glucose production is zero. The rate of glucose metabolism during the insulin infusion can be directly compared under differing physiologic conditions if the concentration of glucose-perfusing, glucose utilizing tissues is the same, that is, the arterial glucose concentrations are matched.

We assessed in vivo insulin action using the euglycemic clamp technique in women with previous gestational diabetes and in nondiabetic women before and during intake of a low-dose ethinyl estradiol–levonorgestrel triphasic oral contraceptives for 6 months.[27] Both groups had normal oral glucose tolerance tests and plasma insulin levels before and during treatment. The glucose metabolic clearance rate and endogenous glucose production were calculated from specific glucose activities. The rates of glucose metabolized during the investigation were similar in both groups before treatment. During hormonal intake the rate of glucose metabolized decreased significantly (27%) in women with previous gestational diabetes, whereas the decrease in normal subjects was less pronounced (17%). Moreover, in the group of normal women, there was a significant negative correlation between glucose uptake during the clamp investigation and the area under the insulin curves calculated from a glucose tolerance test preceding the clamp investigation (Fig. 1). Such a correlation was not found in previous gestational diabetic women, indicating that normal women are perfectly capable of compensating for increased insulin resistance during hormonal intake, whereas the insulin secretion in the previous diabetic women is slightly impaired.

Thus the study showed that in normal women and women with previous gestational diabetes, intake of oral contraceptives may decrease insulin sensitivity, although no change in oral glucose tolerance can be observed. To date only one other clamp study on insulin sensitivity in normal women receiving oral contraceptives has been published. Kasdorf and Kalkhoff[27] applied a euglycemic clamp in seven normal women receiving a low-dose monophasic combination of ethinyl estradiol plus levonorgestrel. After 3 and 6 months a hyperinsulinemic response to oral glucose was observed during oral glucose tolerance tests which is similar to our observations with the same compound.[16] Also, these investigators found a decrease in glucose utilization

rates, expressing decreased insulin sensitivity after steroid intake for 3 months. However, in contrast to our findings, reduced insulin sensitivity in peripheral tissue ameliorated with time and returned to baseline levels after 6 months.

Comment

This review has characterized the current state of knowledge of the influence of oral contraceptives on glucose metabolism at the cellular level. The metabolic effects are unlike other adverse reactions to drugs, insidious, and thus may be unnoticed by both patients and clinicians. However, even discrete changes in glucose metabolism may promote development of coronary heart disease as already discussed. This can partly be explained by the positive correlation between insulin resistance and partly by the influence of hyperinsulinemia on lipid metabolism.[28] Lipid changes associated with hyperinsulinemia are increased total cholesterol and triglycerides and decreased high-density lipoprotein cholesterol values.[29] The effect of hyperinsulinemia on lipid metabolism at the cellular level can be elucidated by results from animal experiments on key enzymes in lipogenesis and lipolysis.[30] Lipogenesis increases because of increased activity of glucose-6 phosphate dehydrogenase, malic enzyme 3-hydroxyacyl-Co A, whereas the activity of the glycolytic enzymes, such as phosphofructokinase, hexokinase, pyroyate kinase, and α-glycerophosphate are unchanged. In addition to inhibition of lipolysis and synthesis of cholesterol, phospholipid and triglyceride exposure of arterial tissue to insulin results in proliferation of smooth muscle cells. More long-term exposure to high concentrations in insulin results in the development of lipid-filled lesions, fatty streaks, which are similar to those seen in early atherosclerosis.[31] These findings indicate the need for long-term integrated studies on glucose and lipid metabolism if the tendency toward more widespread use of oral contraceptives in women >35 years old becomes more manifest. In young healthy women there is no reason to believe that the modern types of combined low-dose oral contraceptives will have any influence on glucose metabolism that will result in any clinical problem.

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Low-dose oral contraceptives and carbohydrate metabolism

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Combined oral contraceptive use has been associated with increased incidence of impaired and diabetic glucose tolerance. Although increased risk of overt symptoms of diabetes has not been associated with oral contraceptive use, increased risk of coronary heart disease has been consistently demonstrated. Diabetes is associated with increased risk of coronary heart disease, especially in women. Elevated plasma glucose and insulin concentrations are also associated with increased risk of coronary heart disease. Studies of the effects of low-dose oral contraceptives on glucose tolerance test plasma glucose and insulin levels are reviewed. Low-dose combined oral contraceptives induced changes in measures of carbohydrate metabolism in directions consistent with increased risk of coronary heart disease. The magnitude of these changes may depend on the dose and type of progestogen. The clinical implications of these changes are unknown, but it would seem advisable to minimize them where possible. (Am J Obstet Gynecol 1990;163:348-53.)

Key words: Combined oral contraceptive, glucose tolerance, insulin, coronary heart disease

When oral contraceptive–induced deterioration in glucose tolerance was observed in the mid-1960s, there was concern that this might increase the risk of diabetes mellitus in oral contraceptive users.[1] Subsequently, major population studies have demonstrated increased prevalence of diabetic oral glucose tolerance tests among oral contraceptive users. In the Walnut Creek Contraceptive Drug Study, there was a 2.0% prevalence of diabetic oral glucose tolerance tests among oral contraceptive users compared with a 1.0% prevalence in nonusers.[2] In the 1976 to 1980 U.S. National Health and Nutrition Examination Survey, there was a 1.7% prevalence among oral contraceptive users compared with a 0.6% prevalence among nonusers.[3] Furthermore, these studies also demonstrated that the prevalence of impaired glucose tolerance was increased more than twofold in oral contraceptive users. Both studies used National Diabetes Data Group criteria for defining diabetes mellitus and impaired glucose tolerance. However, although diabetic and impaired glucose tolerance test profiles have been consistently demonstrated in oral contraceptive users, increased prevalence of overt symptoms of diabetes mellitus has not been observed.[4] Consequently, there has been a tendency for the importance of studies of carbohydrate metabolism in oral contraceptive users to be overlooked. The absence of an association between clinical symptoms of diabetes mellitus and oral contraceptive use may derive from the relatively short duration of follow-up and the young age of the women included in existing epidemiologic studies. Diabetes associated with oral contraceptive use might be expected to develop over a long period in response to sustained deterioration in glucose tolerance and thus may be seen as a past-user effect in older, postmenopausal women. Thus an effect might be seen in modulation of the age-related risk of maturity onset diabetes.

Although the risk of diabetes mellitus associated with oral contraceptive use remains to be effectively explored, the risk of coronary heart disease, as evidenced by myocardial infarction, has been consistently demonstrated. Sixteen studies have shown that oral contraceptive use increases the risk of fatal or nonfatal myocardial infarction either independently or by poten-

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tiating the effects of other risk factors.[5-20] Only two studies have shown no evidence of increased risk.[21, 22] There is also increased risk of coronary heart disease with diabetes mellitus and impaired glucose tolerance.[23-35] Thus the questions arise—could the effects of oral contraceptives on carbohydrate metabolism contribute to the increased risk of coronary heart disease associated with oral contraceptive use? How relevant are these potential associations, established in users of older high-dose oral contraceptives, to current low-dose oral contraceptives?

Carbohydrate metabolism and coronary heart disease

Increased mortality rates in diabetic persons are primarily the result of vascular disease. The risk of coronary heart disease in diabetic persons has been demonstrated in several prospective studies.[23-28] Interestingly, in all except one,[24] diabetic women were at greater risk than diabetic men. Impaired glucose tolerance, which is defined either by established criteria or by the upper percentiles of oral glucose tolerance test glucose concentrations in the cohort under examination, has also been found to be associated with increased risk of coronary heart disease.[29-33] Two such studies have included both men and women, and both showed that women were greater risk than men.[27, 29] Thus although the risk of coronary heart disease with impairment of glucose tolerance has not been as thoroughly studied in women as in men, the few studies that have been carried out suggest that women are at increased risk, perhaps more so than men.

Elevated glucose concentrations may be only a marker for risk of coronary heart disease, or they may be causally related to the development of the pathologic changes underlying coronary heart disease. Glycosylation of apolipoprotein B has been shown to interfere with the catabolism of low-density lipoprotein and the inhibition of cholesterol synthesis by low-density lipoprotein.[34, 35] Thus there are theoretic mechanisms by which deterioration in glucose tolerance could promote atherogenesis and coronary heart disease. A complicating factor, however, is whether the deterioration in glucose tolerance in the epidemiologic studies described is associated with insulin deficiency or insulin excess. In oral contraceptive users deterioration in glucose tolerance has consistently been associated with insulin excess.[36-38] Three studies have examined both insulin and glucose as risk factors for coronary heart disease. The Helsinki Policemen Study of 982 men, ages 35 to 64 years, showed a significant relationship between 9.5-year coronary heart disease incidence (death or nonfatal myocardial infarction) and plasma insulin concentration at 1 and 2 hours after an oral glucose load.[32] The association remained after multivariate analysis. Neither fasting plasma insulin or any of the plasma glucose measures were related to coronary heart disease risk. The Paris Prospective Study of 7038 men, ages 43 to 54 years, showed a significant relationship between 11.2-year coronary heart disease mortality and fasting plasma insulin and plasma insulin concentrations 2 hours after an oral glucose load.[31] In a multivariate analysis only the fasting plasma insulin concentration remained a significant risk factor. The Busselton Study is the only prospective study that examined insulin as a risk factor in both men and women.[29] In this study the 1-hour insulin concentration after an oral glucose load was significantly associated with 6-year incidence of coronary heart disease, 12-year coronary heart disease mortality, and 12-year cardiovascular disease mortality, but only in men, ages 60 to 69 years. Insulin was not a risk factor in younger or older men or in women. However, the 1-hour blood sugar level was significantly related to coronary heart disease and cardiovascular disease mortality in women, ages 60 to 69 years, but not in younger or older women or men. When the 12-year mortality from cardiovascular disease was examined in men and women older than 60 years, there was increasing risk with increasing 1-hour blood sugar and plasma insulin concentrations in men, but only with increasing 1-hour blood sugar level in women. The Busselton Study differs from the Helsinki and Paris studies in that it did not find insulin to be a risk factor for coronary heart disease in men less than 60 years old. The study also differs because it used a lower dose of glucose (50 gm versus 75 gm) for the oral glucose tolerance tests and thus may have been less sensitive to distinguishing variations in insulin response.

The role of insulin as a risk factor for coronary heart disease in women requires further investigation. It is perhaps relevant that in the Framingham Study, which clearly demonstrated that diabetic women are at greater risk of coronary heart disease than are men, almost all women with coronary heart disease took insulin.[23] On the basis of a multivariate analysis of this study, including blood pressure, smoking, and serum cholesterol, they concluded that other factors, as yet unknown, would be needed to account for the higher incidence of cardiovascular disease in diabetic persons. Insulin levels were not included in the multivariate analysis.

The potential role of insulin in atherogenesis has recently been reviewed.[39] Insulin has been shown to promote arterial smooth muscle cell proliferation, stimulate cholesterol synthesis in smooth muscle cell, induce lipid-containing lesions in the arteries of animals fed a normal diet, and augment lipid synthesis in arteries. Arteries also contain receptors specific for the growth-promoting effects of insulin. Thus insulin can be di-

Table I. Low-dose combined oral contraceptive formulations currently in use in the United Kingdom

Formulation	*Code*	*United Kingdom proprietary name*
250 μg levonorgestrel + 30 μg ethinyl estradiol	250LG:30EO	Eugynon-30, Ovran-30
150 μg levonorgestrel + 30 μg ethinyl estradiol	150LG:30EO	Microgynon, Ovranette
1000 μg norethisterone + 35 μg ethinyl estradiol	1000NE:35EO	Norimin, Neocon
500 μg norethesterone + 35 μg ethinyl estradiol	500NE:35EO	Ovysmen, Brevinor
150 μg desogestrel + 30 μg ethinyl estradiol	150DG:30EO	Marvelon
150 μg desogestrel + 20 μg ethinyl estradiol	150DG:20EO	Mercilon
75 μg gestodene + 30 μg ethinyl estradiol	75DG:30EO	Femodene, Minulet
50/75/125 μg levonorgestrel + 30/40/30 μg ethinyl estradiol	50-125LG:30-40EO	Logynon, Trinordiol
500/750/1000 μg norethisterone + 35 μg ethinyl estradiol	500-1000NE:35EO	Trinovum

rectly involved in some of the processes that typically accompany atherogenesis.

Insulin excess will be associated with an inadequate tissue response to insulin, that is, insulin resistance. Reaven[40] and Zavaroni et al.[41] have recently drawn attention to the possible importance of insulin resistance in coronary heart disease risk. Insulin resistance is associated with numerous disturbances that have consistently been linked with increased risk of coronary heart disease. These include impairment of glucose tolerance, hyperinsulinism, elevated very low–density lipoprotein triglyceride concentrations, reduced high-density lipoprotein cholesterol concentrations, and hypertension. The term "syndrome X" has been introduced to encompass this range of disturbances. Whether insulin resistance is primary in the development of coronary heart disease or whether it is an accessory to other predisposing factors remains to be determined.[42] Effective research in this area will depend on the application of techniques that enable accurate quantification of insulin resistance, and several alternatives, including the glycemic clamp and mathematical modeling of glucose tolerance test glucose and insulin concentrations, are now available.[43]

Thus there is evidence that both elevated glucose and insulin concentrations can have direct effects that could further atherogenesis. When elevations in glucose and insulin occur together, they indicate resistance to the action of insulin, which may underly a number of important metabolic changes that indicate increased risk of coronary heart disease. As yet, we have no reason to believe that oral contraceptive–induced insulin resistance with its accompanying elevations in glucose and insulin concentrations is entirely innocent with regard to atherogenesis and coronary heart disease. As in many aspects of coronary heart disease research, the risk in women relating to impairment of glucose tolerance and elevated insulin levels has been inadequately investigated. Although such uncertainty exists, it would seem prudent to clearly define the effects of different oral contraceptive formulations on glucose and insulin levels and favor those that have the least potentially adverse effects on these measures.

Low-dose oral contraceptives and carbohydrate metabolism

A rough distinction may be made between the three eras of oral contraceptives. In the 1960s, the high-dose oral contraceptives containing >50 μg of estrogen predominated; in the 1970s, there were medium-dose oral contraceptives containing 50 μg of estrogen; and in the 1980s, there have been the low-dose oral contraceptives containing <50 μg of estrogen. Two additional developments occurred during the low-dose era, namely, the introduction of phasic oral contraceptives and the introduction of novel progestogens designed to have minimal androgen-like side effects. Some of the most commonly encountered low-dose oral contraceptives are listed in Table I.

In a review of studies of the effects of oral contraceptives on carbohydrate metabolism until 1980, Furman[36] noted that most have shown that high- and medium-dose oral contraceptives could impair glucose tolerance and induce a hyperinsulinemic response to glucose. The effects of low-dose oral contraceptives on glucose and insulin levels have been the subject of sporadic reports, from which it is difficult to obtain a consistent picture. Findings from those studies of normal women taking low-dose oral contraceptives, published in the 1980s and for which oral glucose tolerance test glucose and insulin data were given, are summarized in Table II. Where possible, the incremental area (i.e., the area under the concentration profile but above the basal level) has been used to provide a measure of disturbance in oral glucose tolerance test response unconfounded by changes in the fasting state. All these studies were longitudinal in design, and women acted as their own controls. Almost all claimed that the formulations studied had no effect on carbohydrate metabolism. This is rather surprising when one considers the magnitude of the changes that many observed. For example, two studies[52, 53] conclude that a

Table II. Studies of oral glucose tolerance test glucose and insulin responses in users of low-dose oral contraceptives

Formulation	*Investigators*	*Duration (mo)*	*Nos.*	*Observed effect*
150LG:30EO	Wynn 1982 [44]	3	173	IGA > 55% IIA > 25%
		15	86	IGA > 84% IIA > 25%
		25	39	IGA > 80% IIA > 11%
		37	17	IGA > 236% IIA > 8%
	van der Vange et al., 1987 [45] *Spellacy et al., 1982 [38]	6	10	IGA > 91% IIA > 14%
1000NE:35EO	van der Vange et al., 1987 [45]	6	10	IGA = 0% IIA > 4%
500NE:35EO	Spellacy et al., 1982 [38]	12	12	IGA > 258% IIA > 17%
150DG:30EO	Gaspard et al., 1983 [46]	6	14	GA > 9% IA < 24%
	van der Vange et al., 1987 [45]	6	10	IGA > 418% IIA > 30%
150DG:20EO	Fioretti et al., 1987 [47]	6	17	IGA > 40% IIA > 30%
	van den Ende et al., 1987 [48]	3	13	IGA > 229%
			11	IIA > 46%
		2 mo off	13	IGA > 190%
			11	IIA > 53%
75GD:30EO	Fotherby et al., 1987 [49]	6	13	IGA > 92%
			11	IIA > 12%
50-125LG:30-40EE	Vermeulen and Thiery, 1982 [50]	6	5	GA > 6% IA > 50%
	Gaspard et al., 1983 [46]	6	13	GA > 12% IA < 22%
	Skouby et al., 1985 [51]	2	19	GA > 43% IA < 10%
		6	19	GA > 24% IA < 5%
	van der Vange et al., 1987 [45]	6	10	IGA −1.2 > 2.5† IIA > 41%
500-1000NE:35EO	Toth and Ryan, 1988 [52]	3	7	IGA > 73% IIA < 13%
	Spellacy et al., 1988 [53]	3	35	IGA > 65% IIA > 28%

*Spellacy et al. summarized studies of this formulation carried out during the 1970s. These showed variable effects on glucose tolerance but a consistently elevated insulin response.

†Percentage change could not be calculated; published figures given.

norethindrone-containing triphasic oral contraceptive had no effect on carbohydrate metabolism. Nevertheless, the increases in incremental area under the oral glucose tolerance test glucose concentration profile were 73% and 65%, respectively. In contrast, in a large cross-sectional analysis of oral glucose tolerance test glucose and insulin responses (648 nonuser controls compared with 239 users of a low-dose levonorgestrel-containing oral contraceptive), we have found that a percentage difference of 35% in oral glucose tolerance tests incremental glucose area was highly significant.[54] However, the importance of our study lay in the additional observation that underlying the relatively small, albeit significant, differences in mean incremental glucose and insulin areas were differences in the frequency distribution of oral glucose tolerance test glucose and insulin responses between oral contraceptive users and nonusers that were comparable with differences seen between those at risk of coronary heart disease and those not at risk. Therefore it is not sufficient to conclude on the basis of 10 or 20 patient studies, that if no changes in the oral glucose tolerance test glucose response occurred outside the normal range, there were no important effects on carbohydrate metabolism.

The magnitude of the effects on glucose and insulin levels reported in many studies that claim no effect of low-dose oral contraceptives on carbohydrate metabolism must raise questions about the power of their design. Furthermore, with the exception of the study of van der Vange et al.,[45] no studies have attempted a comparative evaluation of the wide range of low-dose oral contraceptives currently available. In the recently completed study by our group,[55] 1127 women each re-

ceived an oral glucose tolerance test with measurement of plasma glucose, insulin, and C-peptide. Users of five monophasic- and two triphasic-combined oral contraceptives and two progestogen-only oral contraceptives were included in the study. Combination oral contraceptives contained an average estrogen dose of 30 to 35 μg and thus differed primarily in the progestogen content. In the combined oral contraceptive groups, the glucose and insulin responses during the oral glucose tolerance tests were significantly higher than among the control subjects. These differences remained after standardization for age and weight and selection of control groups for each oral contraceptive group, which did not differ significantly in cigarette smoking, alcohol intake, exercise habit, family history of diabetes or heart disease, and the time period over which testing was carried out. Furthermore, there was a consistently observed effect of progestogen dose on the glucose and insulin response. Levonorgestrel- and norethindrone-containing oral contraceptives each contained identical doses of estrogen, but a low or high progestogen dose. Although relative differences were small, the higher progestogen dose had the greatest impact in every case. There was also a trend depending on the type of progestogen. Among the monophasic oral contraceptives the levonorgestrel-containing formulations had the greatest impact, followed by the norethindrone- and desogestrel-containing formulations. With the exception of the high-dose levonorgestrel formulation, in which there was a relatively low response, the C-peptide concentration responses confirmed the relative differences in insulin response and demonstrated that underlying the elevated insulin levels were increases in pancreatic insulin secretion. Furthermore, the relative impact of the different oral contraceptives on carbohydrate metabolism paralleled the relative impact on measures of lipid metabolism. This study suggests that there may be coordinated changes throughout a range of metabolic variables in response to low-dose oral contraceptives, with the magnitude of these changes depending on the dose and type of progestogen.

We conclude that even with the introduction of low estrogen doses, phasic formulations, and new progestogens, the impact of combined oral contraceptives on carbohydrate metabolism remains an important issue. Future studies will need to pay particular attention to the statistical power and the population from which the study group is drawn and will need to incorporate several different formulations to make effective comparisons. Evaluation of a wide range of metabolic changes will be required in each study, for example, changes in lipoproteins and measures of hemostasis. As long as uncertainty remains over the implications of these effects for risk of diabetes mellitus and coronary heart disease, it will be necessary to evaluate thoroughly the metabolic impact of each oral contraceptive and develop formulations or regimens that minimize this impact.

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Some aspects of the relationship between oral contraceptives, lipid abnormalities, and cardiovascular disease

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Most epidemiologic studies suggest an association between current use of combined oral contraceptives and certain manifestations of cardiovascular disease. Most of the data relate to older preparations little used today. Decreased levels of high-density lipoprotein cholesterol and increased amounts of low-density lipoprotein cholesterol were common findings with the older formulations. More recent experimental and epidemiologic data suggest that the potential risk of cardiovascular disease in oral contraceptive users is hardly predicated on an arteriosclerosis basis but related more to thromboembolic events. Because changes in the serum lipid profile are often associated with alterations in the factors of hemostasis, it seems reasonable to suggest the use of preparations void of profound changes in lipid metabolism, especially when other means of efficacy are available inclusive of the newer low-dose oral contraceptives. When risk factors for cardiovascular disease are present, determination of total cholesterol is desirable. In subjects with elevated serum cholesterol, a serum lipid profile should be determined. A woman at risk of cardiovascular disease should be carefully monitored, and repeated lipid determinations are recommended. (Am J Obstet Gynecol 1990;163:354-8.)

Key words: Oral contraceptives, cardiovascular disease, serum lipids

It is well established that certain abnormalities in lipid and lipoprotein metabolism are linked to increased events of cardiovascular disease (CVD). In this respect, most epidemiologic data emphasize high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL). In addition, data suggest the corresponding apolipoproteins, that is, apolipoprotein B for LDL and apolipoprotein A_1 and A_2 for HDL, behave in a similar manner. Combinations of these abnormalities might further augment the risk of CVD.

In general serum cholesterol levels have also been documented to have a clear relationship with CVD, and pharmacologic lowering of cholesterol has resulted in decreased events of CVD at least in men.[1, 2] Accumulating evidence also suggests serum triglycerides as an important risk factor in women.[3, 4] Data from Framingham imply that triglycerides constitutes a risk factor only in women with low HDL cholesterol levels (Fig. 1).[5] In most nonpharmacologic conditions, very low–density lipoprotein (VLDL) and HDL display an inverse relationship. Oral administration of estrogens elevates both VLDL and HDL, and progestogens tend to have opposite effects. Pharmacologically induced alterations in which VLDL and HDL move in the same direction are more difficult to interpret as a function of risk of CVD. Further data on this issue seem highly warranted.

Several other risk factors for CVD have been identified. Sex, age, ethnic group, and family history cannot be influenced, whereas others are potentially changeable. Among such factors one finds smoking, blood pressure, obesity, diet, and sedentary life-style. Some of these risk factors also comprise serum lipid abnormalities, as well as smoking and obesity. In addition, a number of chronic diseases, for example, diabetes, have also been identified as risk factors. The combination of two or more risk factors increases the risk almost exponentially. Therefore it is not surprising that cardiovascular events in oral contraceptive (OC) users are less uncommon in elderly obese or smoking women and that the incidence of CVD varies throughout the world as indicated by a World Health Organization study.[6]

CVD could principally follow from two different mechanisms. Deep venous thrombi could be formed as a result of changes in the coagulation cascade, and emboli from a thrombus may cause a sudden event.

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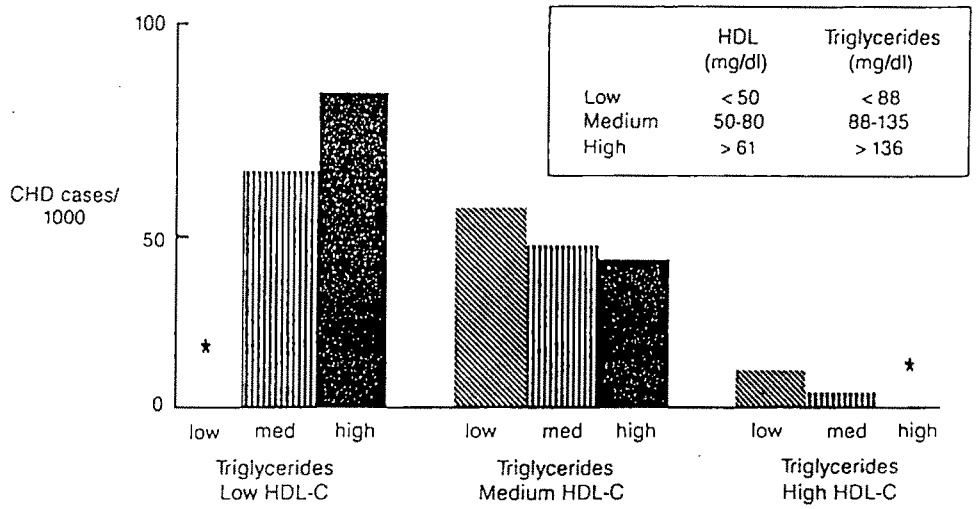


Fig. 1. Incidence of coronary heart disease *(CHD)* in relation to levels of HDL cholesterol *(HDL-C)* and triglycerides. *Groups with <86 persons at risk. (From Castelli WP, et al. Am Heart J 1986;112:432-7.)

Table I. Percent changes in cholesterol and triglycerides in serum, that is, total, and in HDL and LDL after oral medication with unopposed EE; figures are adjusted for sample size, duration of study, and pretreatment endocrine situation

	Dose (μg)	*Studies*	*Change in*			
			Cholesterol			*Triglycerides*
			Total	*HDL*	*LDL*	*Total*
EE	10	2	−12	+5	−12	+30
	20	3	−7	+18	−15	+66
	30	1	−11	+22	−20	+71
	35	1	−6	+16	−12	+68
	50	3	+1	+28	−16	+70

Pertinent evidence also suggests an association between coagulation factors and serum lipid constituents. Hypertriglyceridemia frequently accompanies high levels of fibrinogen and factor X, as well as low fibrinolytic activity.[7] In vitro studies suggest further that increasing concentrations of cholesterol promote platelet aggregation.[8]

A second mechanism by which CVD can occur is by way of atherosclerosis. Vascular lesions could exist before OC medication or develop during OC use as a result of the aging process or even enhanced by OC use, possibly by way of changes in lipid metabolism or alterations induced in the vessel wall.

OC medication induces ovulation inhibition, which almost abolishes endogenous ovarian steroid production. Early menopause, natural or surgical, has been shown to be associated with an increased risk of CVD and alterations in lipid metabolism. It cannot be ruled out with certainty that lack of endogenous steroids has no role in the development of CVD in OC users. Contraceptive steroids given to women undergoing oophorectomy may help distinguish this mechanism further.[9] In principle ethinyl estradiol (EE) tends to increase plasma content of cholesterol, as well as triglycerides, phospholipids, and apolipoproteins. This is reflected in serum lipoproteins as increased levels of HDL and VLDL and at higher doses of LDL. A similar pattern is observed during pregnancy. Lower doses of estrogens, including EE, and early pregnancy seem to decrease LDL levels, but HDL and VLDL are still augmented. However, in all examples, the HDL/LDL cholesterol ratio is above 1 compared with normally menstruating women in whom the ratio is slightly below 1.[10]

EE differs from natural estrogens especially in its ability to augment triglycerides (Table I). This may imply a more marked inhibition of hepatic lipase by the alkylated estrogen. This enzyme is also involved in HDL turnover as exemplified by its importance in the removal of HDL_2 particles from plasma. After EE, triglycerides are elevated not only in VLDL but also substantially in LDL and HDL. In contrast to natural es-

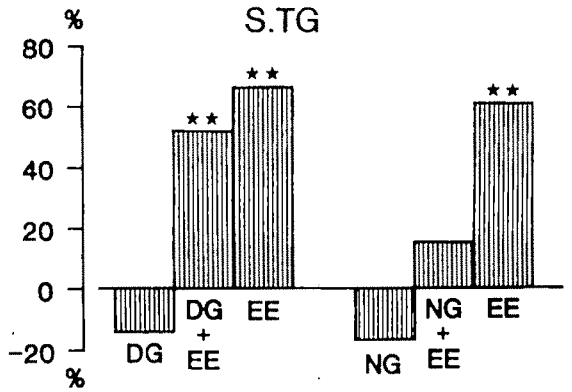


Fig. 2. Percent change in serum triglyceride *(STG)* levels after administration of two 19-nor teststerone derivatives, (*DG*, Desogestrel; *NG*, levonorgestrel) 150 μg/day, orally, in combination with 30 μg of EE and after EE alone (30 μg).[13]

trogens and normal pregnancy, alterations in the molar composition of lipoprotein particles seem to be more marked after EE. This renders the use of Friedwald's formula more difficult because serum triglyceride levels influence the calculation of LDL cholesterol.[11]

It is difficult to assess if the differences observed between EE and natural estrogens should be ascribed the chemical dissimilarity or are merely functions of differences in receptor interactions or pharmacokinetic and pharmacodynamic behavior.

Because all commercially available OCs contain EE (or its methyl ether, mestranol, which is rapidly converted to EE), the differences in lipid metabolic response must be the result of the amount administered and the type and dose of the corresponding progestogen. Lipid metabolic effects by progestogens in OC users could either be androgenic, antiestrogenic, or possibly progestogenic. So far it has been difficult to demonstrate clearly any lipid metabolic effects solely because of effects mediated by way of the progestogen receptor.[12] Because all progestogens downregulate the quantity (and quality?) of estrogen receptors, an antiestrogenic effect is common in all progestogens. Androgenicity has also been demonstrated to be most pronounced for the older 19-nor testosterone derivatives, norethisterone and levonorgestrel, but less so for 17-alpha-hydroxy progestogens and the newer 19-nortestosterone derivates, such as desogestrel, gestodene, and norgestimate. Antiestrogenic effects by progestogens require the simultaneous presence of an estrogen. In studies of women having oophorectomy, levonorgestrel, desogestrel, and cyproterone acetate have similar effects on, for example, serum triglycerides when given alone. However, in combination with the corresponding estrogen as in commercially available OCs, obvious dissimilarities can be amply demonstrated (Fig. 2).

A possible explanation is the differences in antiestrogenicity by the three progestogens. Nonetheless, the concentration of hormone receptors in the liver cannot readily explain the marked effects on liver-derived serum constituents as influenced by exogenous sex steroids. A nonreceptor or nongenomic-mediated effect must also be postulated, such as inhibition or activation of existing hepatic enzyme systems.[12]

In the so-called Royal College of General Practitioners Study,[15] increasing the dose of norethisterone or levonorgestrel seemed to increase the number of CVD events despite the constant dose of the corresponding EE. It was an intriguing thought at the time to compare these data on arterial disease with those obtained from the same preparations on HDL cholesterol. However, several later observations indicated that it was too simple an analogy.

Nonetheless, this observation focused on the progestogen component as also being at least partly responsible for arterial disease and provoked enhanced interest in the development of new progestational agents with higher selectivity and sensitivity for the progestogen receptor. Desogestrel seems to differ from levonorgestrel particularly in its antiestrogenic activity,[13] and rather, preparations containing desogestrel or gestodene increase HDL and decrease LDL. Long-term epidemiologic data on CVD with these preparations are to date unavailable.

Modern prescribing routines and avoiding smoking have made arterial disease in pill users a rare event, which renders epidemiologic studies difficult if aimed at describing the differences between various low-dose preparations.[15]

If cardiovascular events were mediated solely by an atherosclerotic process, possibly as a result of low HDL and high LDL, increased risk should develop after prolonged use. However, this was not the case in the Royal College of General Practitioners Study.[16] In addition, one would expect a higher incidence of CVD in former users. This too has not been verified.[17] Because arteriosclerosis is a rather slow process that develops over years, a sudden event, such as a myocardial infarction or stroke, is commonly preceded by symptoms such as angina pectoris or transient ischemic attack in subjects with an arteriosclerotic platform for their manifestation of CVD. There is no evidence to suggest that the use of OCs influences the incidence or prevalence of angina pectoris.

In a recent study on monkeys in which HDL was reduced by OCs and they were given an atherogenic diet, no excess cardiac atherosclerosis was found when compared with control animals.[18]

In a recent epidemiologic report covering mortality among OC users from 1977 to 1982, Porter et al.[15] observed 11 deaths from CVD in the nonuser group,

Table II. Tentative schedule for screening of OC users regarding cardiovascular disease if family history indicates presence of risk factors for CVD, serum total cholesterol should be assessed, if elevated, a serum lipid profile is performed, which may show a CVD risk pattern, if after 6 months use of OCs this pattern has not improved, an alternate contraceptive method should be considered

Elevated		Normal
Fastings S-TG, S-CHOL, HDL-CHOL		
Risk pattern	No risk pattern	Annual follow-up
New lipid profile 6 months		
	Annual follow-up	
No change or reduced	Increased	
Annual follow-up	Reconsider contraceptive method	

STG, Serum triglycerides; *S-CHOL,* serum cholesterol.

whereas no deaths occurred among users. If the experimental data on lipid metabolism achieved by use of the newest formulations also hold true for the outcome of CVD, it would seem pertinent to suggest that as with postmenopausal replacement therapy, OC use would also protect from CVD, provided that the person is a nonsmoker.

Indeed, a study from Finland[19] implies such a possibility, and the ongoing epidemiologic study from Oxford, England,[20] points in this direction. Clearly, more evidence is needed before any firm position can be taken in regard to newer formulations of OCs and their interrelations with CVD. It should also be pointed out that during the 1960s, OCs were given to women in whom a pregnancy was highly undesirable and therefore often included women at risk of various diseases and of low socioeconomic status. Today other means of efficacious contraception are available, and women with potential risk factors are less likely to be prescribed an OC. For this reason these subjects are more prone to be found among the controls in modern epidemiologic studies on OCs, whereas the opposite was probably true during the 1960s.

It seems prudent that the use of OCs is not associated with any major risk of arteriosclerosis. Nonetheless, formulations with a "negative" influence on HDL and LDL should possibly be avoided. Even if the "atherogenic" lipoprotein pattern is of less relevance for the development of arteriosclerosis in OC users, it does indicate an altered metabolic situation that possibly can be avoided with the use of newer formulations. As previously indicated, lipid metabolic variables are also linked to hemostasis. This also includes prostacyclin and thromboxane A_2. So far data on thromboxane B_2 and 6-keto prostaglandin $F_{1\alpha}$, which are the stable metabolites of thromboxane A_2 and prostacyclin, are inconclusive in regard to the influence by OCs. However, it has been shown repeatedly[21, 22] that both estrogens and progestogens as components of OCs influence the relative content of prostaglandin-precursor fatty acids.

On the basis of current literature, a lipid screening of all potential OC users cannot be recommended. When family history suggests the presence of risk factors for CVD, serum total cholesterol should be determined. If it is elevated, a serum lipid profile should be obtained consisting of fasting serum cholesterol triglycerides and HDL cholesterol. This approach allows the estimation of LDL cholesterol according to Friedwald's formula.

If an OC is prescribed to a woman with risk factors, total cholesterol should be checked annually. If elevated cholesterol is present before OC use, a serum lipid profile should preferrably be carried out after 6 to 8 months and then annually (Table II).

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Estrogenic effect of gestodene- or desogestrel-containing oral contraceptives on lipoprotein metabolism

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In a randomized comparative study, changes in lipoprotein metabolism during the use of two low-dose oral contraceptives with similar doses of ethinyl estradiol but with different progestogenically active compounds were evaluated for their effective estrogen/androgen balance. Sixty-eight healthy women who did not take hormonally active drugs or were pregnant the previous 3 months took either 75 μg of gestodene + 30 μg of ethinyl estradiol or 150 μg of desogestrel + 30 μg ethinyl estradiol during 12 cycles. During the first three cycles serum levels of the following parameters increased: triglycerides, cholesterol in high-density lipoprotein, and apolipoproteins A_1, A_2, and B. Additional increase was observed in apolipoprotein B only after three and six cycles. The induced changes were not significantly different in the two groups, and the levels generally remained within normal limits. The changes seen with both pills reflect a mild estrogenic dominance. On the basis of current knowledge, moderately altered lipoprotein metabolism is not expected to impose an extra risk of atherosclerosis. (AM J OBSTET GYNECOL 1990;163:358-62.)

Key words: Gestodene, lipoproteins, oral contraceptives

High plasma levels of low-density lipoprotein (LDL) cholesterol[1] and its apolipoprotein B[2] and low levels of high-density lipoprotein (HDL) cholesterol[3, 4] and its apolipoproteins A_1 and A_2[5-7] are associated with an increased incidence of ischemic heart disease. LDL is a direct cause of atherogenesis, but the role of HDL in this process is still uncertain. Thus changing LDL levels by intervention will probably alter cardiovascular prognosis, and changing HDL levels will possibly alter cardiovascular prognosis.

Women have a sixfold lower incidence of myocardial infarctions than do men by age 50 years.[8] This advantage declines thereafter. It is conceivable that this advantage is due to the effects of estrogens on lipoprotein metabolism. Postmenopausal oral estrogen therapy is indeed associated with a reduced risk of myocardial infarction,[9] and this therapy causes a decrease in LDL cholesterol[10] and an increase in HDL cholesterol.[11] However, it is also conceivable that testosterone exerts a harmful effect on cardiovascular prognosis in men ("male disadvantage"). Androgens have an HDL cholesterol–lowering effect.[12] Thus HDL levels reflect the balance of estrogenic/androgenic effects (es-

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Table I. Effect of two low-dose OCs on serum triglyceride and lipoprotein lipid levels (range and median or mean ± SD, mmol/L)

	GTD-EE				*DSG-EE*			
Cycle (n)	*0 (32)*	*3 (32)*	*6 (31)*	*12 (29)*	*0 (28)*	*3 (28)*	*6 (26)*	*12 (26)*
TG (range)	0.33-2.00	0.47-2.23	0.43-2.75	0.60-1.87	0.39-1.41	0.57-2.12	0.57-2.42	0.71-2.24
median	0.73	0.95	1.11	1.24	0.73	1.07	1.05	1.28
*p**	<0.001	NS	NS		<0.001	NS	NS	
LDL-ch	2.92	2.77	2.74	2.79	3.01	2.71	2.77	2.74
Mean SD	0.75	0.74	0.72	0.52	0.64	0.49	0.64	0.61
p	NS	NS	NS		<0.05	NS	NS	
HDL-ch	1.32	1.50	1.45	1.49	1.38	1.48	1.51	1.48
Mean SD	0.32	0.32	0.32	0.37	0.30	0.23	0.26	0.27
p	<0.001	NS	NS		<0.01	NS	NS	

TG, Triglyceride; *LDL-ch,* low-density cholesterol; *HDL-ch,* high-density cholesterol.
*Change of mean value different from zero (Wilcoxon rank test).

Table II. Effect of two low-dose OCs on serum apolipoprotein levels (mean ± SD, mg/dl)

	GTD-EE				*DSG-EE*			
Cycle (n)	*0 (32)*	*3 (32)*	*6 (29)*	*12 (28)*	*0 (28)*	*3 (28)*	*6 (26)*	*12 (25)*
Apo A_1	163	184	179	186	163	183	187	192
SD	21	23	21	21	27	28	33	33
*p**	<0.001	NS	NS		<0.001	<0.05	NS	
Apo A_2	63 ($p < 0.05$)†	73	63 ($p < 0.01$)	74 ($p < 0.05$)	67	77	78	81
SD	9	9	9	9	9	10	12	12
p	<0.001	NS	<0.05		<0.001	NS	NS	
Apo B	89	99	106	113	92	101	108	114
SD	21	26	25	23	19	21	24	22
p	<0.001	<0.05	<0.05		<0.001	<0.05	<0.05	

Apo, Apolipoprotein.
*Change in mean value different from zero (Wilcoxon rank test).
†Difference of mean value from corresponding mean value in DSG-EE-group (Mann-Whitney).

trogen/androgen balance). Progestogens can have antiestrogenic or androgenic effects,[13-15] depending on the particular biologic test model. This implies that progestogens may modify the estrogenic effects of ethinyl estradiol and may also influence the estrogen/androgen balance in oral contraceptive (OC) preparations.

We applied these principles to the effects of two OCs with the same dosage of estrogen but with a different progestogenic compound.

Methods

Subjects. Sixty-eight healthy women, ages 20 to 35 years, not pregnant or taking OCs for at least 3 months, were randomly allocated into two groups receiving either 75 μg of gestodene + 30 μg of ethinyl estradiol (GTD-EE) or 150 μg of desogestrel + 30 μg of ethinyl estradiol (DSG-EE). Fasting blood samples for lipoprotein lipid and apolipoprotein determinations were obtained during the pretreatment period and after 3, 6, and 12 cycles, between the eighteenth and twenty-second day of the cycle, between 8:00 AM and 10:00 AM.

Informed consent was obtained. The Committee on Medical Ethics of the University of Leiden approved this study.

Serum lipid levels were determined by standard methods. LDL cholesterol was calculated according to Friedewald.[16] Apolipoproteins A_1 and A_2 were determined according to Cheung and Albers[17] and LDL apolipoprotein B according to Havekes et al.[18]

Statistics. To test for significant difference from zero, the Student *t* test for paired (for changes within group) and unpaired observations (for differences between groups) was used when the results were normally distributed. Otherwise, the Wilcoxon rank test and Mann-Whitney U test were used, respectively.

Results

Eight subjects did not complete this study. The reason for dropping out was not related to the use of OCs.

Table I shows the effects on the serum levels of (lipoprotein) lipids and apolipoproteins during OC use. Between the first three cycles, a significant increase in triglyceride levels was noted in both OC groups. After the third cycle, no further increase in triglyceride levels was found. Triglyceride levels in the two groups were

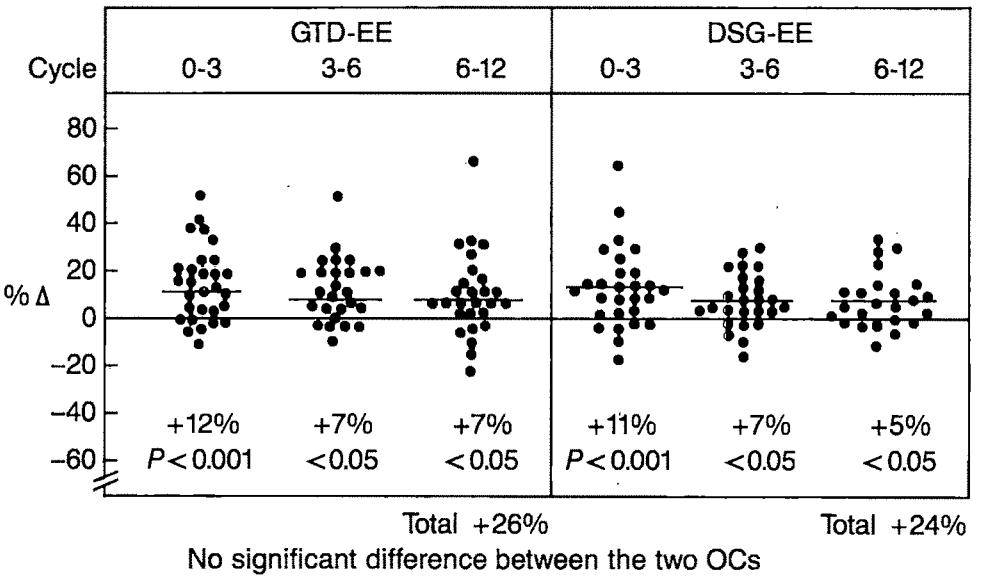


Fig. 1. Individual variations in LDL apolipoprotein B levels from pretreatment to cycle 3, 6, and 12 (percentage of previous value).

Table III. Effect of two low-dose OCs on the composition of LDL and HDL (mean, mmol/gm protein)

	GTD-EE				*DSG-EE*			
Cycle (n)	*0 (32)*	*3 (32)*	*6 (29)*	*12 (28)*	*0 (28)*	*3 (28)*	*6 (26)*	*12 (25)*
LDL-cholesterol	3.3	2.8	2.7	2.5	3.3	2.7	2.6	2.4
LDL-apo B								
*p**		<0.001	0.032	0.013		<0.001	0.023	0.005
HDL-chol	0.58	0.58	0.58	0.57	0.59	0.57	0.57	0.54
Apo A_1 + A_2								
p		NS	NS	NS		NS	NS	NS

Apo, Apolipoprotein.
*Change in mean value different from zero (Wilcoxon rank test).

not significantly different in the four periods of observation.

LDL cholesterol values did not increase during use of these OC preparations; in the DSG-EE group even a slight but significant decrease was found during the first three cycles, although this effect became nonsignificant during the following cycles. The HDL values increased significantly during the first three cycles in both groups—by 14% in the GTD-EE group and by 7% in the DSG-EE group. No further change in these values after three cycles was observed until 1 year. In all four periods of observation no significant difference was found between the two groups in LDL and HDL cholesterol levels. In Table II the effects on serum apolipoprotein levels are shown. The baseline levels in the two groups were in good agreement with each other, except for apolipoprotein A_2, which was significantly higher in the DSG-EE group. A highly significant increase in all apolipoproteins was found during the first three cycles of OC use in both groups. After the third cycle LDL apolipoprotein B but not apolipoprotein A_1 and A_2 increased further in both groups. The increase in apolipoprotein B was significant during each period of observation and is shown in more detail in Fig. 1. The range in percentage change in LDL apolipoprotein B between the twelfth cycle and the pretreatment period was 1% to 69% in the GTD-EE group and −11% to 85% in the DSG-EE group. At the sixth cycle a dip in the apolipoprotein A_2 pattern occurred in the GTD-EE group. Except for apolipoprotein A_2 levels at the end of the sixth cycle, no difference in the effect of the two OC preparations on apolipoprotein levels was found.

As shown in Table III, the composition of the lipoproteins appeared to change in LDL only, that is, an apparent depletion of cholesterol relative to the protein moiety, apolipoprotein B. In HDL the components changed by the same percentage, which indicates that in these women the ratio between HDL_2 and HDL_3 remained constant.

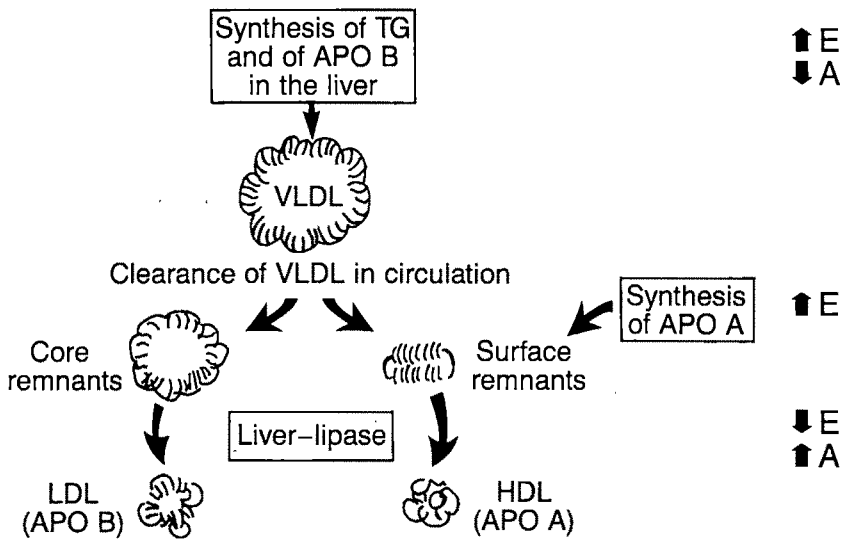


Fig. 2. Effect of estrogens *(E)* or antiestrogens/androgens *(A)* on lipoprotein metabolism: a simplified scheme. Triglyceride *(TG)* synthesis in the liver is enhanced by E and inhibited by A. Production of VLDL and its apolipoprotein B *(apoB)* follows that of TG. During intravascular delipidation of VLDL, remnants appear in the circulation. Remnants of the core are converted into LDL by liver lipolytic activity *(LLA)* of liver lipase; surface remnants take up apolipoprotein A *(apo A)*. Synthesis of apoA is enhanced by E. Resulting particles are converted into HDL_2 and subsequently (by LLA) into HDL_3. LLA is inhibited by E and enhanced by A. For the effects of oral contraceptives, see text.

Comment

The effect of GTD-EE and DSG-EE on lipoprotein metabolism was apparently similar. The changes were in agreement with earlier studies performed by us[15] and others.[19] The consequence of these findings on cardiovascular risk is unknown, but on the basis of current knowledge, it seems unlikely that the induced changes increase the risk. Serum levels of the two lipoproteins possibly involved in atherogenesis remained within normal limits. If the epidemiologic findings of apolipoproteins A_1[5] and B[2] in relating to the incidence of coronary heart disease can be applied to these data in women (the former negatively and the latter positively correlated with the incidence in men), then the increase in risk by the rise in apolipoprotein B should be offset by the decrease in risk resulting from the rise in apolipoproteins A_1 and A_2.[20] The rise in triglyceride level is probably of very little relevance[21] for risk, if at all.

The mechanism of the estrogenic/androgenic effect on lipoprotein levels is only partly understood. Estrogens enhance both the triglyceride synthesis rate in the liver[22-24] and subsequently that of very low–density lipoprotein (VLDL). This explains the rise in serum triglyceride levels. It may be postulated that the rate of synthesis of the main carrier apolipoprotein of VLDL, apolipoprotein B, is also increased.[25] As VLDL is converted to LDL in the circulation, the rise in LDL apolipoprotein B levels may be explained as a consequence of its increased formation (i.e., an estogenic effect). It should be noted that the technique of measuring apolipoprotein B applied in this work excludes VLDL apolipoprotein B and only allows the LDL apolipoprotein B to penetrate the radial immunodiffusion gel.[18]

The increase in HDL levels may be explained partly by the enhancement of apolipoprotein A_1 synthesis by estrogens.[25] On the other hand, clearance of HDL may be hampered because liver lipase activity is probably inhibited by the estrogenic effect[26] of both preparations (Fig. 2).

In LDL the increase in apolipoprotein B relative to LDL cholesterol caused a lowering of the ratio of LDL cholesterol/apolipoprotein B. This can also be explained by assuming that the liver lipase activity (Fig. 2) is inhibited[15, 26] during OC use. Thus the conversion of core remnants of VLDL to LDL may be reduced, resulting in an accumulation of LDL precursors and cholesterol-poor/triglyceride-rich LDL particles as found in congenital liver lipase activity deficiency.[27] An alternative hypothesis is that the enhancement of VLDL production[22-24] by the estrogenic effect of OC caused an increase in apolipoprotein B turnover and apolipoprotein B levels, whereas in the circulation the filling of the particles with cholesterol ester[28] lagged behind.

In HDL no change in composition was found, which suggests that the ratio between the two subfractions HDL_2 and HDL_3 remained constant. Thus the expected

liver lipase activity inhibition, if any, apparently failed to cause accumulation of HDL_2 (Fig. 2).

In conclusion the low-dose OC preparations studied here and earlier[15] show evidence of an estrogenic dominance in their effect on lipoprotein lipid and apolipoprotein levels. After six cycles, LDL apolipoprotein B still significantly increases, which indicates that the (V)LDL transport reaches a new set point after only 12 cycles. Thus studies on the ultimate effect of OC on lipoprotein metabolism require at least 1 year.

During low-dose OC use, lipoprotein levels in most patients remain within desirable limits. The two OCs studied do not differ in the degree of changes brought about in these levels. The impact of these changes on the risk of atherogenesis is probably minor, if at all.

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Time-dependent alterations in lipid metabolism during treatment with low-dose oral contraceptives

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The effect of sex steroids on lipid metabolism depends on the type and dose of the compounds, the route of administration, and the duration of treatment. Therefore the composition of an oral contraceptive determines the resultant effect on lipids and lipoproteins. During 12 months of treatment, the effects of two oral contraceptives containing 30 μg of ethinyl estradiol and 150 μg of desogestrel (EE/DG) or 75 μg of gestodene (EE/GSD) on 19 serum parameters of lipid metabolism were followed in 11 women each. There was no change in total cholesterol and phospholipids. Total triglyceride levels were significantly elevated only by EE/GSD. After 3 and 6 months of intake of both preparations, a transitory increase in the triglyceride content of very low–density lipoprotein and low-density lipoprotein and a decrease in low-density lipoprotein–phospholipids was observed. After 12 months, very low–density lipoprotein cholesterol, very low–density lipoprotein phospholipids, and apolipoprotein B were significantly elevated, whereas very low–density lipoprotein triglycerides and all components of low-density lipoprotein were unchanged. Most of the components of high-density lipoprotein (HDL) were increased as a result of a rise in HDL_3 and apolipoprotein A_2, whereas HDL_2 and apolipoprotein A_1 were not altered. There was no significant difference between the effects of the two preparations, although those of EE/GSD were mostly more pronounced. The increase in high-density lipoprotein, very low–density lipoprotein, and total triglycerides reflects a slight preponderance of the effect of the estrogen component. Because low-density lipoprotein cholesterol and total cholesterol were not changed, treatment with both formulations is in all probability not associated with an elevated risk of atherosclerosis. (Am J Obstet Gynecol 1990;163:363-9.)

Key words: Low-dose oral contraceptives, desogestrel, gestodene, ethinyl estradiol, lipids, lipoproteins

A series of investigations has demonstrated that sex steroids may influence lipid metabolism. The changes in lipid levels and the composition of lipoproteins are dependent on the type and dose of the compounds, the route of administration, and the duration of treatment.[1-5] With respect to steroid dose and the route of administration, it must be emphasized that the steroid concentration circulating through the liver determines the effect. Although transdermal estrogen replacement therapy is regarded as ineffective, it has been shown that percutaneous and subcutaneous treatment with high doses of estradiol, resulting in estradiol levels of more than 200 pg/ml, increases high-density lipoprotein cholesterol and reduces low-density lipoprotein cholesterol similar to oral treatment with low-dose estradiol.[6,7]

The changes in lipid parameters mainly reflect the hepatic effects of sex steroids. Estrogens stimulate the production of triglycerides, very low–density lipoprotein, HDL_3, and apolipoproteins A_1, A_2, and B in the liver,[8-10] enhance the synthesis of hepatic B:E and E receptors, which are important for the clearance of intermediate-density lipoprotein, low-density lipoprotein, and chylomicron remnants,[11-13] inhibit hepatic triglyceride lipase, which degrades the triglycerides and phospholipids of HDL_2,[14] and increase the lecithin content of phospholipids.[15,16] Most of these effects are antagonized by progestogens, particularly by nortestosterone derivatives, on account of their antiestrogenic or androgenic properties. Progestogens inhibit the hepatic production of triglycerides, very-low–density lipoprotein, and apolipoprotein A_1, stimulate the activity of hepatic triglyceride lipase, and decrease the lecithin content of phospholipids.[16-18]

Therefore the composition of the pill is responsible for the resultant effect on lipids and lipoproteins. The higher the dose of ethinyl estradiol, the higher are the levels of total triglycerides, whereas the progestogen component exerts only a modulatory effect. The type and dose of the progestogen, however, determines the effect on low-density lipoprotein cholesterol, which is supposed to be a risk factor for the development of atherosclerosis. Levonorgestrel increases this lipopro-

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Table I. Dependency on composition of oral contraceptives of changes in lipid metabolism[1, 3, 4]

Formulation	*CH*	*TG*	*HDL-CH*	*HDL_2-CH*	*LDL-CH*	*Apo B*	*Apo A_1*
50 EE/1000 NET	+7%	+45%	—	—	+6%		+9%
50 EE/1000 EDD	+9%	+57%	—	—	+10%		+11%
35 EE/1000 NET	+9%	+24%	—	—	+15%	+30%	+12%
35 EE/1000 EDD	+9%	+38%	—	—	+10%	+29%	+19%
50 EE/250 LNG	+8%	+32%	−13%	−27%	+18%		−9%
30 EE/250 LNG	—	+17%	−21%				
20 EE/250 LNG	—	+17%	−21%				
30 EE/150 LNG	—	+15%	−10%				

EE, Ethinyl estradiol; *NET,* norethisterone; *EDD,* ethynodiol diacetate; *LNG,* levonorgestrel; *CH,* cholesterol; *TG,* triglycerides; *HDL-CH,* high-density lipoprotein cholesterol; *HDL_2-CH,* high-density $lipoprotein_2$ cholesterol; *LDL-CH,* low-density lipoprotein cholesterol; *Apo B,* apolipoprotein B; *Apo A_1,* apolipoprotein A_1.

Table II. Effect of a triphasic preparation containing 30 μg of ethinyl estradiol + 50 μg levonorgestrel, 40 μg ethinyl estradiol + 75 μg levonorgestrel, and 30 μg ethinyl estradiol + 125 μg levonorgestrel on various serum parameters of lipid metabolism

Total CH	—	VLDL-CH	—	LDL-CH	—		—
Total TG	+16%*	VLDL-TG	+17%	LDL-TG	+9%	HDL-TG	+52%
Total PL	+7%*	VLDL-PL	—	LDL-PL	+19%*	HDL-PL	—
Lp(a)	—	Apo B	+8%			Apo A_1	+18%*
						Apo A_2	+37%*
						HDL_3-CH	+6%*

From März W, Gross W, Gahn G, Romberg G, Taubert H-D, Kuhl H. Am J Obstet Gynecol 1985;153:287-93.
See Table I for abbreviations.
*$p < 0.05$.

tein fraction more than norethisterone, whereas ethynodiol diacetate has a minor effect (Table I).[1, 3, 4] On the other hand, the higher the dose of levonorgestrel, the more pronounced is the reduction in high-density lipoprotein cholesterol, whereas preparations containing norethisterone or ethynodiol diacetate have nearly no effect.

However, it is possible to counterbalance this adverse effect of levonorgestrel on lipid metabolism by a proper composition of the pill. Triphasic formulations containing ethinyl estradiol and levonorgestrel have been shown not to decrease high-density lipoprotein cholesterol and not to increase low-density lipoprotein cholesterol; the effects on various serum parameters of lipid metabolism even indicate a slight overweigh of the estrogen component (Table II).[19]

The introduction of the new progestogens, desogestrel, norgestimate, and gestodene, with high progestogenic but relatively low androgenic activities, rendered it possible to reduce the ethinyl estradiol dose of monophasic pills to 30 μg or less without an adverse change in the lipoprotein pattern. The present study considered the effects of two low-dose oral contraceptives containing 30 μg of ethinyl estradiol and 150 μg of desogestrel (EE/DG) or 75 μg of gestodene (EE/GSD) on 19 serum parameters of lipid metabolism during 12 months of treatment.

Material and methods

Twenty-two normal healthy volunteers with regular menstrual cycles who were between 18 and 35 years old participated in the study. Informed consent was obtained. The women had not used hormonal contraceptives for at least 3 months before the study and were not under interfering pharmacologic therapy. An internal and gynecologic examination, including a Papanicolaou smear, was carried out before subject selection. During a control cycle, ovulation was confirmed to have probably taken place by the determination of serum progesterone (>3 ng/ml).

Two groups of 11 women each were randomly assigned to take preparation containing 30 μg of ethinyl estradiol and 75 μg of gestodene (Schering AG, Berlin, Federal Republic of Germany) or that containing 30 μg of ethinyl estradiol and 150 μg of desogestrel (Organon GmbH, Oberschleissheim, Federal Republic of Germany) for 12 months.

Blood samples were taken by venipuncture after overnight fasting between 8:00 and 10:00 AM (i.e., 24 hours after first pill intake) on days 1, 10, and 21 of the first, third, sixth, and twelfth treatment cycle and of the control cycle preceding the first treatment cycle. Each sample was drawn into tubes containing ethylenediaminetetraacetic acid · K_2 (1.5 to 2 mg/ml). Plasma was prepared by low-speed centrifugation

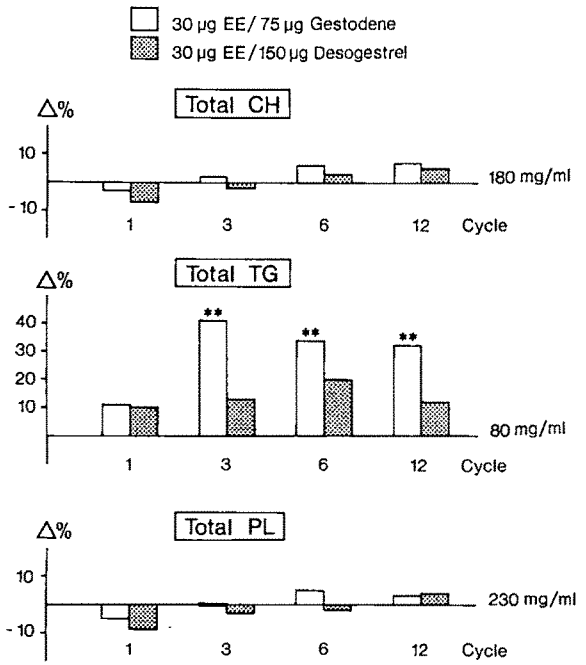


Fig. 1. Average changes (%) in the serum levels of total cholesterol *(CH)*, triglycerides *(TG)*, and phospholipids *(PL)* during 12 months of treatment with EE/GSD or EE/DG. Average control values are given at the end of the abscissa. ** $p < 0.01$ versus controls.

(1500 × *g*, 30 minutes) and kept at 4° C during storage. All determinations of lipoproteins were completed within 1 week after blood collection.

Cholesterol (CHOD-PAP-Method), triglycerides (GPO-PAP), and phospholipids were determined using reagents from Boehringer (Mannheim, Federal Republic of Germany). Very low–density lipoproteins were quantified in their lipid constituents after preparative ultracentrifugation at d < 1.00 gm kg/L.[20] High-density lipoproteins were determined after phosphotungstate/$MgCl_2$ precipitation of apolipoprotein B–containing lipoproteins, and high-density lipoprotein subfractions HDL_2 and HDL_3 were resolved by ultracentrifugation in the respective supernatants at d = 1.125 kg/L as previously described.[21] Low-density lipoproteins were calculated as differences between total lipids and high-density lipoprotein + very low–density lipoprotein. Apolipoproteins A_1 and A_2 were quantified by zone immunoelectrophoresis,[22] and apolipoprotein B was measured by conventional radialimmunodiffusion with NOR partigen plates (Behringwerke AG, Marburg, Federal Republic of Germany).

Data were analyzed by multivariate analysis of variance (repeated measures design) for the comparison of EE/DG versus EE/GSD or by the Student paired *t* test for the comparison of treatment cycles versus control cycles or of different treatment cycles.

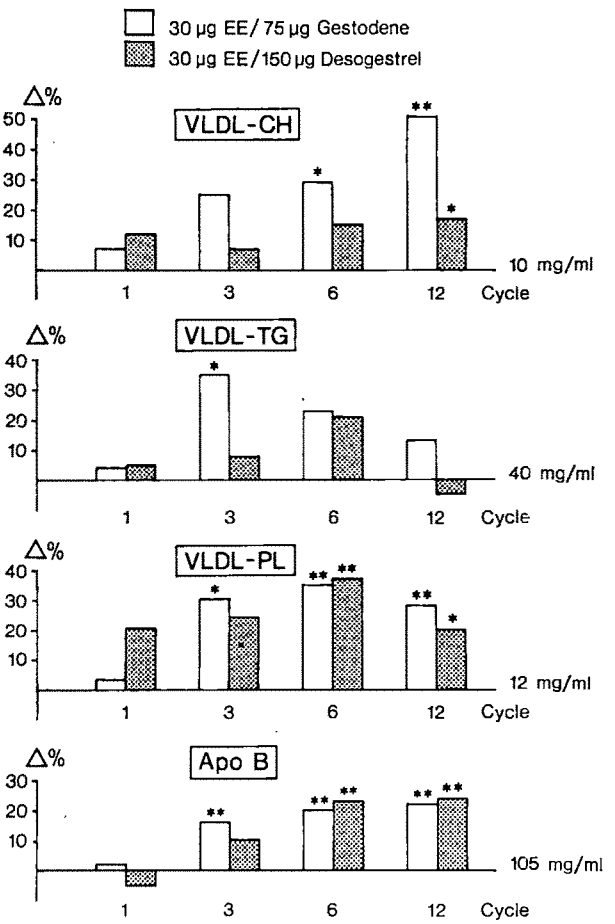


Fig. 2. Average changes (%) in the serum levels of very low–density lipoprotein cholesterol *(VLDL-CH)*, very low–density lipoprotein triglycerides *(VLDL-TG)*, very low–density lipoprotein phospholipids *(VLDL-PL)*, and apolipoprotein B *(Apo B)* during 12 months of treatment with EE/GSD or EE/DG. Average control values are given at the end of the abscissa. * $p < 0.05$; ** $p < 0.01$ versus controls.

Results

The determination of lipids and lipoprotein components, which was carried out three times during the control cycle and 12 times during the year of treatment in each of 22 volunteers, revealed great intra- and interindividual variations. Therefore no significant difference between the effects of both oral contraceptives on lipid metabolism could be found.

The changes observed in some parameters during treatment were to a certain degree dependent on time. In most cases there was no effect during the first treatment cycle, whereas during the following cycles various significant alterations became discernible compared with the control cycle. On the other hand, some significant changes that occurred during the first treatment cycle disappeared during the following treatment period.

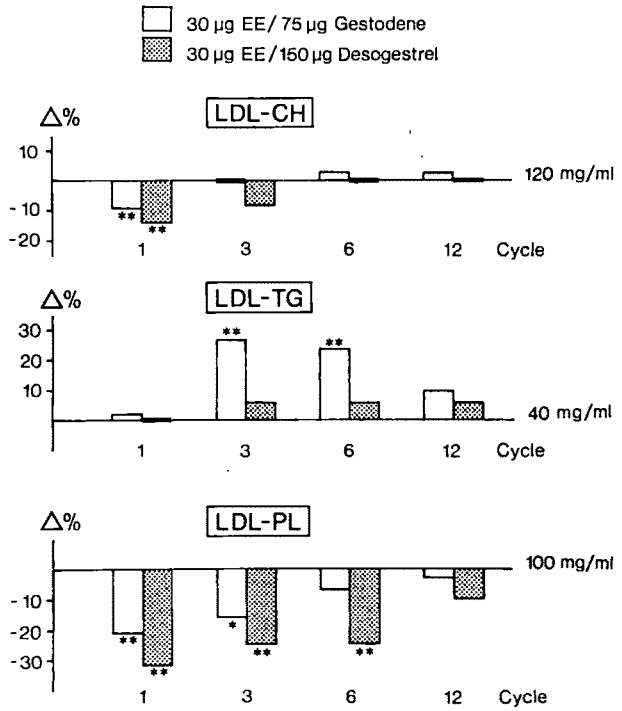


Fig. 3. Average changes (%) in the serum levels of low-density lipoprotein–cholesterol *(LDL-CH)*, low-density lipoprotein–triglycerides *(LDL-TG)*, and low-density lipoprotein–phospholipids *(LDL-PL)* during 12 months of treatment with EE/GSD or EE/DG. Average control values are given at the end of the abscissa. * $p < 0.05$; ** $p < 0.01$ versus controls.

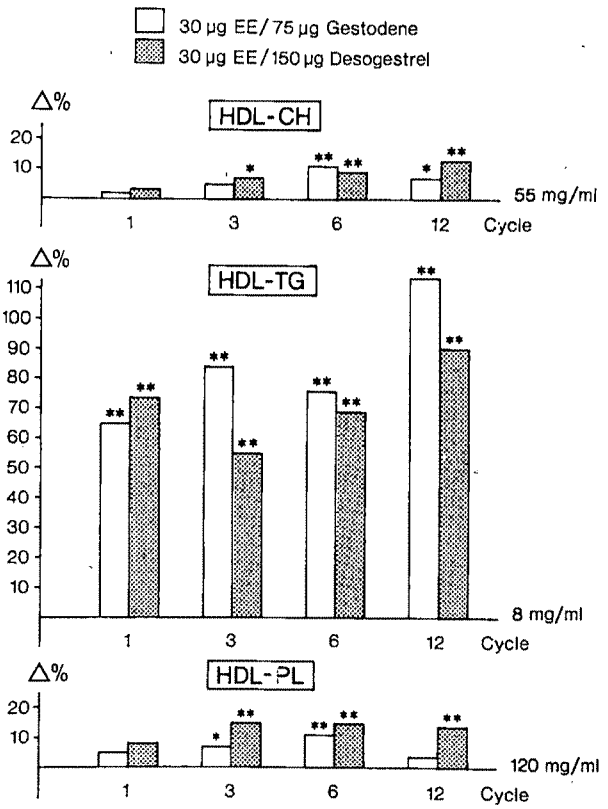


Fig. 4. Average changes (%) in the serum levels of high-density lipoprotein cholesterol *(HDL-CH)*, high-density lipoprotein triglycerides *(HDL-TG)*, and high-density lipoprotein phospholipids *(HDL-PL)* during 12 months of treatment with EE/GSD or EE/DG. Average control values are given at the end of the abscissa. * $p < 0.05$; ** $p < 0.01$ versus controls.

There was no influence of both preparations on total cholesterol and phospholipids, whereas total triglycerides were considerably elevated with EE/GSD ($p < 0.01$) and moderately but not significantly with EE/DG (Fig. 1).

The cholesterol content of very low–density lipoprotein was increased after 6 and 12 months; the effect was more pronounced during treatment with EE/GSD. There was also a significant increase in very low–density lipoprotein phospholipids and in apolipoprotein B, wheres that of very low–density lipoprotein triglycerides was only transitory (Fig. 2).

Low-density lipoprotein cholesterol and low-density lipoprotein phospholipids were significantly decreased during the first treatment cycle, but thereafter the effect extenuated and disappeared after 12 months of treatment. The increase in low-density lipoprotein triglycerides during the third and sixth month of intake of EE/GSD was also only transitory (Fig. 3).

There was a significant increase in the cholesterol, triglyceride, and phospholipid content of high-density lipoprotein and in the level of apolipoprotein A_2 during intake of both formulations, which was mainly because of an increase in HDL_3 (Figs. 4 and 5). Contrary to this, there was no change in HDL_2 and apolipoprotein A_1 except a transitory elevation in HDL_2 cholesterol and phospholipids during the first month of intake of EE/GSD (Fig. 6).

Comment

The present study demonstrates an increase in total triglycerides, very low–density lipoproteins, and apolipoprotein B, indicating an overweigh of the effects of the estrogen component on lipid metabolism because estrogens have been shown to stimulate very low–density lipoprotein synthesis and secretion.[23] The effects were considerably more pronounced during treatment with EE/GSD, although the differences compared with those of EE/GD are not significant as a result of the great intra/interindividual variations. A similar elevation in the triglyceride levels of 20% to 40%,[24-31] of 25% to 55% in the very low–density lipoprotein components,[25] and of 20% to 40%[27, 32] in the apolipoprotein B concentrations during treatment with EE/DG has previously been reported, even though several investigators did not observe a change in very low–density lipoprotein or apolipoprotein B.[27, 30, 31]

Most of these studies that had been carried out for 6 months confirm our findings that treatment with

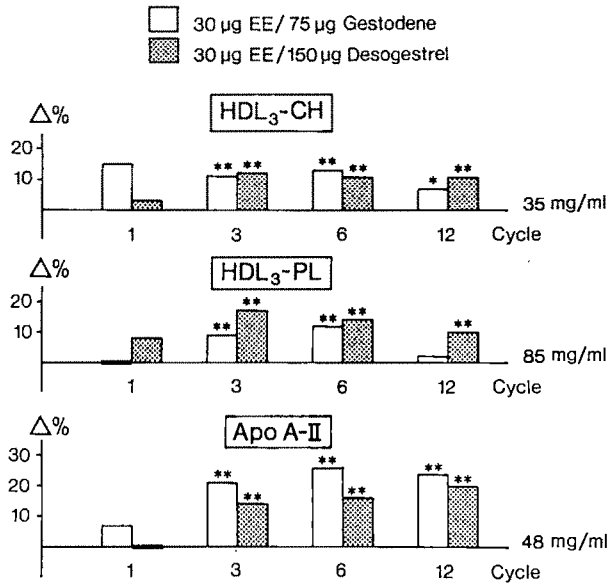


Fig. 5. Average changes (%) in the serum levels of HDL_3 cholesterol, HDL_3 phospholipids, and apolipoprotein A_2 during 12 months of treatment with EE/GSD or EE/DG. Average control values are given at the end of the abscissa. * $p < 0.05$; ** $p < 0.01$ versus controls.

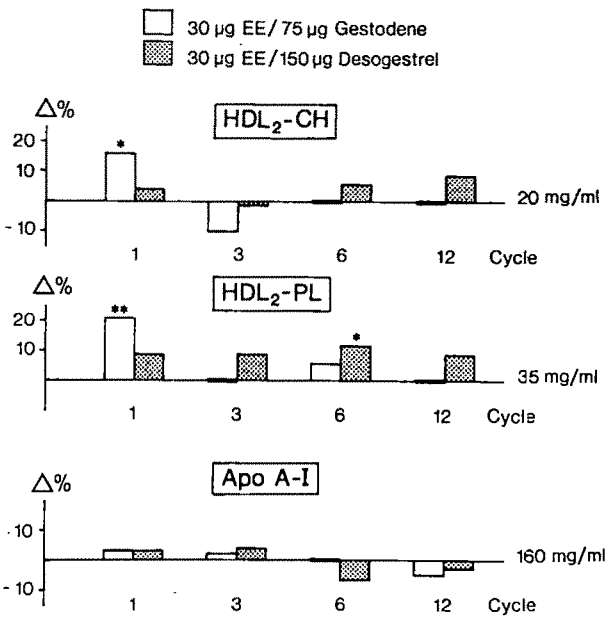


Fig. 6. Average changes (%) in the serum levels of HDL_2 cholesterol, HDL_2 phospholipids, and apolipoprotein A_1 during 12 months of treatment with EE/GSD or EE/DG. Average control values are given at the end of the abscissa. * $p < 0.05$; ** $p < 0.01$ versus controls.

EE/DG has no influence on low-density lipoprotein levels.[24, 25, 27, 28, 32] The significant rise in low-density lipoprotein after 3 and 6 months of intake of EE/GSD and the decrease in low-density lipoprotein phospholipids with both preparations was only transitory and disappeared after 12 months. This indicates an influence of the duration of treatment, reflecting a type of adaptation of some metabolic steps. A time-dependent change in the lipoprotein pattern during intake of a low dose ethinyl estradiol–containing and levonorgestrel-containing oral contraceptive has previously been reported.[33] However, the maintenance of elevated triglycerides, very low–density lipoprotein, and apolipoprotein B levels demonstrates that the stimulation of hepatic synthesis of these parameters continues during 12 months of treatment. Because of the enhanced secretion of very low–density lipoprotein, the enhanced hydrolyzation of very low–density lipoprotein triglycerides by the lipoprotein lipase in muscle and fat tissue leads to an increased formation of low-density lipoprotein by way of intermediate-density lipoprotein. In the present study, low-density lipoprotein levels remain unchanged, indicating that increased formation might be counterbalanced by enhanced clearance of intermediate-density lipoprotein in the liver. The cholesterol/triglyceride ratio was elevated in the very low–density lipoprotein fraction and decreased in the low-density lipoprotein fraction. This could be interpreted as reflecting a rise in the levels of intermediate-density lipoprotein and remnants, which are assumed to play a role in the development of atherosclerosis. Contrary to this, the increase in hepatic B:E and E receptors allows enhanced removal of intermediate-density lipoprotein, low-density lipoprotein, and remnants from the circulation.[11-13] Moreover, there is no evidence that long-term intake of oral contraceptives promotes the development of atherosclerosis.

The preponderance of the effect of the estrogen component in both preparations is also reflected by the increase in high-density lipoprotein, because progestogens with their pronounced androgenic activity decrease serum high-density lipoprotein cholesterol in a dose-dependent manner.[34] Treatment with both EE/DG and EE/GSD resulted in a small but significant rise in nearly all components of high-density lipoprotein. The effect was based on a rise in HDL_3 and apolipoprotein A_2, which is mainly contained in HDL_3, whereas HDL_2 and apolipoprotein A_1 were not altered. An increase in HDL_3 but not in HDL_2 during intake of EE/DG has also been previously observed.[27, 31, 32] Contrary to this, our results of apolipoprotein A_1 do not agree with those of several studies, which showed an increase of 20% to 30%.[27-32]

The rise in HDL_3 and apolipoprotein A_2 levels is probably caused by an enhanced hepatic synthesis stimulated by ethinyl estradiol, whereas progestogens seem to be ineffective.[35, 36] On the other hand, progestogens may counteract ethinyl estradiol–stimulated apolipoprotein A_1 production.[33] Because of the elevated supply

with the substrate, an enhanced peripheral lipolysis of very low–density lipoprotein leads to an increased conversion of HDL_3 to HDL_2 through assimilation of cholesterol, phospholipids, and apolipoproteins from triglyceride-rich particles.[37] Because HDL_2 levels remained unchanged, this might be compensated by an enhanced degradation by hepatic triglyceride lipase. It has been demonstrated that treatment of postmenopausal women with desogestrel does not influence enzyme activity,[18] but it cannot be excluded that desogestrel and gestodene may abolish the inhibitory effect of ethinyl estradiol on the hepatic triglyceride lipase. HDL_2 had been shown to be the major substrate of the hepatic lipase, whereas very low–density lipoprotein triglyceride is hydrolyzed to a much lesser extent.[14] However, the enzyme may also play a role in the catabolism of smaller triglyceride-rich lipoproteins along the very low–density–intermediate-density–low-density lipoprotein pathway.[30]

The results clearly show that the risk of developing atherosclerosis, as far as the lipoprotein pattern is concerned, is not elevated during treatment with the two low-dose preparations. Rather, the slight increase in most of the high-density lipoprotein components and probably enhanced removal of atherogenic intermediate-density lipoprotein and remnants indicate a beneficial effect. It should be remembered that high-density lipoprotein stimulates not only reverse cholesterol transport but also inhibits smooth muscle cell proliferation, stimulates endothelial cell prostacyclin biosynthesis, facilitates the catabolism of triglyceride-rich lipoproteins, and possibly facilitates fibrinolysis.[39]

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Effects of three combined oral contraceptive preparations containing desogestrel plus ethinyl estradiol on lipid metabolism in comparison with two levonorgestrel preparations

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The effects of three different desogestrel-containing combined oral contraceptive preparations on lipid metabolism were compared with those of two levonorgestrel preparations. The following preparations were studied: (1) monophasic desogestrel (150/30), (2) monophasic desogestrel (150/20, containing 20 μg of ethinyl estradiol instead of 30 μg of ethinyl estradiol, (3) biphasic desogestrel, (4) monophasic levonorgestrel (150/30), and (5) triphasic levonorgestrel. The effects of these preparations were assessed on high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein A-I, apolipoprotein B, the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol, and the ratio of apolipoprotein A-I to apolipoprotein B after 3 months of treatment, and the percentage changes with regard to pretreatment were calculated. The monophasic desogestrel (150/30) and biphasic desogestrel preparations induced higher high-density lipoprotein cholesterol and apolipoprotein A-I levels than did their levonorgestrel-containing counterparts. Low-density lipoprotein cholesterol levels were increased in monophasic levonorgestrel and clearly decreased in the lowest ethinyl estradiol–containing monophasic desogestrel (150/20) and biphasic desogestrel preparations. Apolipoprotein B increased in all preparations. The antiatherogenic indexes (ratios of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol and apolipoprotein A-I to apolipoprotein B were higher for monophasic desogestrel (150/30) and biphasic desogestrel than for comparable levonorgestrel-containing preparations. The differences seen between the desogestrel and levonorgestrel preparations can best be explained by the lower intrinsic androgenicity of 3-keto-desogestrel (active metabolite of desogestrel) than that of levonorgestrel. (Am J Obstet Gynecol 1990;163:370-3.)

Key words: Desogestrel, lipid metabolism, oral contraceptives

The two constituents of combined oral contraceptives have counteracting effects on various lipid parameters. Ethinyl estradiol increases triglycerides, high-density lipoprotein cholesterol, and its major apolipoprotein, whereas low-density lipoprotein cholesterol is decreased. Progestogens, especially those derived from nortestosterone, have opposite effects on these parameters. Larsson-Cohn et al.[1] showed that for levonorgestrel-containing preparations, the ratio ethinyl estradiol to levonorgestrel determines the final effect on various lipid parameters.

In 1981 an oral contraceptive preparation containing the new progestogen, desogestrel (150 μg), in combination with 30 μg of ethinyl estradiol, was introduced. In comparative studies[2,3] it appeared that this oral contraceptive preparation induces a higher high-density lipoprotein cholesterol level than a similar combination of levonorgestrel and ethinyl estradiol. This difference is attributed to the less intrinsic androgenicity of 3-keto-desogestrel (the active metabolite of desogestrel) compared with that of levonorgestrel.[4] Another oral contraceptive preparation containing 150 μg of the progestogen, desogestrel, in combination with only 20 μg of ethinyl estradiol, was marketed in 1988. Furthermore, a biphasic preparation containing approximately

Table I. Composition and regimen of the oral contraceptive preparations used in the present study

Preparation		*Regimen*
Biphasic desogestrel	7 days	25 μg DSG + 40 μg EE
	14 days	125 μg DSG + 30 μg EE
Monophasic desogestrel (150/30)	21 days	150 μg DSG + 30 μg EE
Monophasic desogestrel (150/20)	21 days	150 μg DSG + 20 μg EE
Monophasic levonorgestrel	21 days	150 μg LNG + 30 μg EE
Triphasic levonorgestrel	6 days	50 μG LNG + 30 μg EE
	5 days	75 μg LNG + 40 μg EE
	10 days	125 μg LNG + 30 μg EE

DSG, Desogestrel; *LNG*, levonorgestrel; *EE*, ethinyl estradiol.

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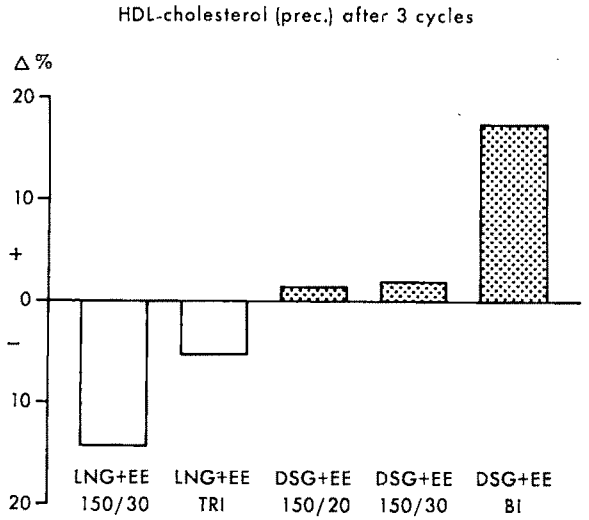


Fig. 1. Percentage change in high-density lipoprotein cholesterol (precipitation method) during treatment with the various combinations of oral contraceptives studied. *Open bars* are levonorgestrel preparations and *dotted bars* desogestrel preparations (see Table I for composition and intake regimen of the preparations). *HDL,* High-density lipoprotein; *LNG,* levonorgestrel; *EE,* ethinyl estradiol; *DSG,* desogestrel.

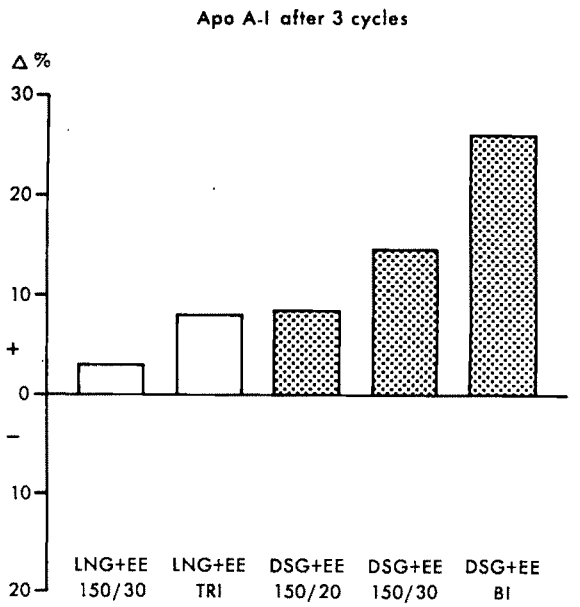


Fig. 2. Percentage change in apolipoprotein A-I *(apo A-I)* during treatment with the various combinations of oral contraceptives studied (see Fig. 1 for explanation about bars and abbreviations).

30% less desogestrel than that in the monophasic preparations is in development. In past years several well-controlled studies were performed with these preparations, in which levonorgestrel preparations were used as reference to assess the effects on lipid metabolism. In this article we give a survey of our findings to see whether we can observe certain trends in effects on lipid metabolism in relation to the composition of the various preparations. We discuss the effects of the three desogestrel-containing preparations on some important lipid parameters (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein A-I, apolipoprotein B, and the ratios high-density lipoprotein cholesterol to low-density lipoprotein cholesterol and apolipoprotein A-I to apolipoprotein B) in comparison with those of monophasic and triphasic levonorgestrel preparations.

Material and methods

All women participating in the various studies were in good general health and without contraindications for oral contraceptives. They were 20 to 36 years of age with regular menstrual cycles and had no hormonal treatment 2 months before the start of the study. During the study, they did not receive any medication and were not allowed to change their life-style with respect to alcohol consumption, exercise, and smoking. Table I shows the composition of the oral contraceptives used and the intake regimen given.

Blood samples were taken after overnight fasting before the start of treatment and in the third treatment cycle on one of the last 3 days of tablet intake. Blood was collected in tubes containing ethylenediaminetetraacetic acid as anticoagulant and plasma was prepared according to a routine laboratory procedure. Serum was also prepared. All lipid assessments were carried out as previously described.[5]

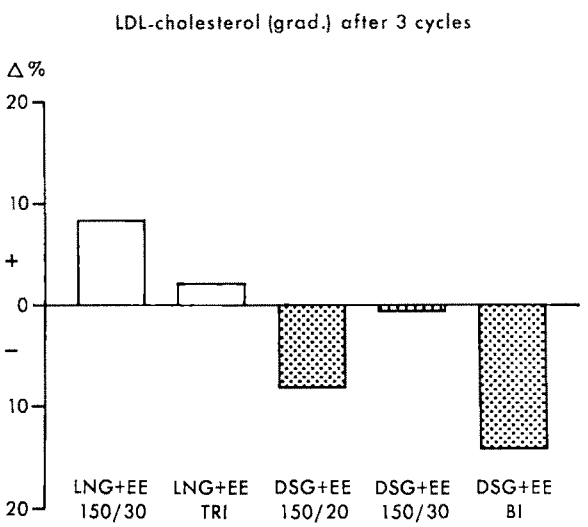


Fig. 3. Percentage change in low-density lipoprotein cholesterol (isolated by gradient centrifugation) during treatment with the various oral contraceptive combinations studied (see Fig. 1 for explanation about bars and abbreviations). *LDL,* low-density lipoprotein.

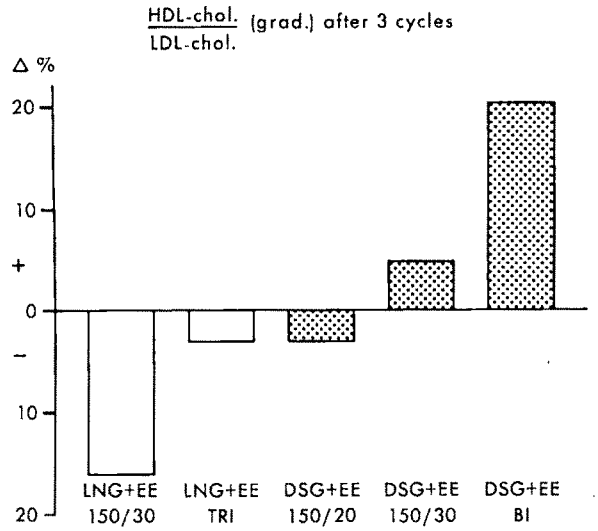


Fig. 4. Percentage change in the calculated ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol (both isolated by gradient centrifugation) with the various oral contraceptive combinations (see Fig. 1 for explanation about bars and abbreviations).

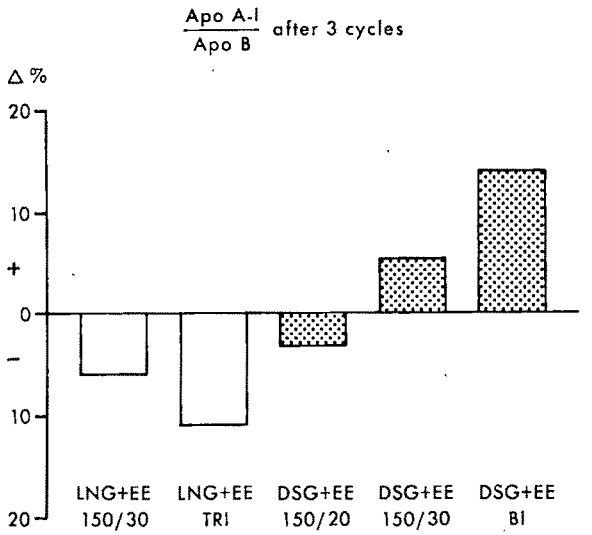


Fig. 5. Percentage change in the calculated ratio of apolipoprotein A-I *(apo A-I)* to apolipoprotein B *(apo B)* with the various oral contraceptive combinations studied (see Fig. 1 for explanation about bars and abbreviations).

Table II. RBAs of levonorgestrel and 3-keto-desogestrel for the progesterone and androgen receptors in intact MCF-7 cells and their selectivity indexes (ratio RBA progesterone receptor to that of androgen receptor)

	Progesterone receptor (Org 2058 = 100%)	*Androgen receptor (DHT = 100%)*	*Selectivity index*
3-keto-desogestrel	260	6.5	40
Levonorgestrel	135	15.3	8.8

From Kloosterboer et al. Contraception 1988;38:325-32, with permission of Butterworth Publishers.

Results

The effects of the various preparations on high-density lipoprotein cholesterol are illustrated in Fig. 1. A clear decrease in high-density lipoprotein cholesterol is observed with monophasic levonorgestrel. A reduction in the amount of levonorgestrel of approximately 30% as in triphasic levonorgestrel gives a smaller decrease in high-density lipoprotein cholesterol. The use of desogestrel as progestogen in two monophasic preparations gives a slight increase in high-density lipoprotein. Reducing the amount of desogestrel as in the biphasic preparation shows a further increase in high-density lipoprotein cholesterol. The apolipoprotein A-I levels increase for all preparations studied as seen in Fig. 2. We measured total apolipoprotein A-I levels in these studies, and because a small contribution of apolipoprotein A-I may be derived from serum fractions other than high-density lipoprotein, no decrease was observed for any of the preparations studied. Most likely the contribution to apolipoprotein A-I of these fractions is more or less similar for the various preparations, since the same trend is seen for apolipoprotein A-I as for high-density lipoprotein cholesterol.

The changes in low-density lipoprotein cholesterol are seen in Fig. 3. An increase in this atherogenic parameter is found for monophasic levonorgestrel, whereas no change is observed for the monophasic desogestrel (150/30) preparation. Surprisingly, the other monophasic desogestrel (150/20) shows a decrease. The increase in low-density lipoprotein cholesterol is less pronounced for triphasic levonorgestrel than for monophasic levonorgestrel, but its desogestrel-containing counterpart shows a clear decrease.

The apolipoprotein B levels measured in serum were increased for all preparations and did not show the trend found for low-density lipoprotein cholesterol (results not shown). The antiatherogenic indexes, ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol, and ratio of apolipoprotein A-I to apolipoprotein B were calculated, because various investigators believe that these parameters are the best indicators of cardiovascular risk. Both parameters

(Figs. 4 and 5) give the same pattern: a clear decrease in values for monophasic levonorgestrel, whereas the values for biphasic desogestrel show a profound increase.

Comment

The best explanation for the difference in effects on high-density lipoprotein between desogestrel preparations and comparable levonorgestrel preparations can be found in the lower intrinsic androgenicity of 3-keto-desogestrel compared with that of levonorgestrel.

Table II[4] shows the relative binding affinities for the progesterone and androgen receptors of the two progestogens. The calculated selectivity index for 3-keto-desogestrel is far higher than that of levonorgestrel.

Kuusi et al.[6] showed that the two progestogens, desogestrel and levonorgestrel, have a different effect on hepatic lipase. This enzyme is involved in the catabolism of HDL_2 and it is stimulated by levonorgestrel. Consequently, lower high-density lipoprotein cholesterol and apolipoprotein A-I, the major apolipoprotein of high-density lipoprotein, will be found for the levonorgestrel preparations compared with the desogestrel preparations. The difference in intrinsic androgenicity of the two progestogens is likely to be responsible for the difference in effect on low-density lipoprotein cholesterol. Reducing the dose of levonorgestrel as in the triphasic preparation diminishes the effects on lipid metabolism, whereas lowering the dose of desogestrel as in the biphasic preparation further improves the effects on lipid metabolism. Thus both the type and dose of the progestogen are important for the final effect on lipid metabolism.

The lower androgenicity of 3-keto-desogestrel makes it possible to reduce the amount of ethinyl estradiol to 20 μg without substantially impairing the lipid profile. Castelli[7] showed that high levels of high-density lipoprotein and low low-density lipoprotein decrease the risk of coronary heart disease in women.

In light of these observations, it can be concluded that oral contraceptive preparations with a good lipid profile (high high-density lipoprotein and low low-density lipoprotein) have an advantage. Therefore the better antiatherogenic indexes found with the desogestrel prepartions compared with those for the levonorgestrel preparations can be considered beneficial.

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Metabolic changes during treatment with two different progestogens

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Two triphasic oral contraceptives containing the same amount of ethinyl estradiol in combination with gestodene or levonorgestrel were compared with respect to contraceptive effect, cycle control, and effects on lipid metabolism and coagulation. Serum concentrations of gestodene, levonorgestrel, ovarian and pituitary hormones, and sex hormone–binding globulin were measured. Thirty-three healthy women were randomized into two groups receiving either of the preparations. Before treatment and in the third and sixth cycles, blood sample were drawn in the morning while subjects were still in bed to obtain basal conditions. The contraceptive effect and cycle control were good with both preparations, and there were only a few minor side effects. Sex hormone–binding globulin was elevated twofold in the levonorgestrel group and threefold in the gestodene group. The gestodene concentration in serum varied more than the levonorgestrel concentration, but with correction for variations in sex hormone–binding globulin binding, less variability in gestodene and levonorgestrel concentrations were seen. High-density lipoprotein$_2$ cholesterol decreased in the levonorgestrel group but was unchanged in the gestodene group, whereas apolipoprotein A_1 increased in the gestodene group but not in the levonorgestrel group. Antithrombin III decreased in the gestodene group but was unchanged in levonorgestrel-treated women. Factor VII increased in both groups but more in the gestodene group. We conclude that gestodene has a positive influence on lipid metabolism, probably because of its lower androgenicity, and a slightly negative influence on coagultion. The latter, however, probably has no clinical relevance. (Am J Obstet Gynecol 1990;163:374-7.)

Key words: Oral contraceptives, lipid metabolism, blood coagulation

During the past 25 years, oral contraceptives (OCs) have been improved continuously with respect to decreasing the dose of total steroid content and the introduction of new progestogens in an attempt to minimize adverse effects and provide contraception safety. Several epidemiologic studies[1-3] have established a connection between OC use and an increased risk of cardiovascular and thromboembolic diseases. The changes in lipid metabolism and hemostatic parameters leading to these serious adverse effects are dependent on the dose and type of steroids, especially progestogens.

The aim of this longitudinal study performed under basal conditions was to compare the clinical effects and changes in endogenous hormones, lipid metabolism, and coagulation in two groups of women receiving either the new progestogens gestodene (GES) or levonorgestrel (LNG) in combination with the same amount of ethinyl estradiol (EE). The changes were correlated with serum concentrations of the progestogens.

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Material and methods

Thirty-three women requesting OCs volunteered to participate in this study. The participants were 19 to 36 years old, with normal weight and blood pressure, healthy, and with regular menstrual cycles. None had used hormonal treatment or had been pregnant 3 months before the study. The women were randomized into two groups receiving a triphasic preparation of either GES or LNG in combination with the same amount of EE (Table I). OC intake started on the first day of menstruation and was of 21 days' duration, followed by 7 days of withdrawal.

Blood samples were drawn in the luteal phase of the cycle before treatment (values that served as controls) and during the third and sixth cycles of medication. Basic conditions were ensured by drawing blood samples 24 hours after the last dose of medication and after overnight fasting while women were still at home in bed. Blood samples were centrifuged, and serum was stored at −20° C until analyzed.

The concentration of hormones was measured by radioimmunoassay, and sex hormone–binding globulin (SHBG) was measured by an immunoradiometric assay. Triglyceride and cholesterol levels were measured by enzymatic methods, and the remaining lipids

Table I. Dosage regimen of the two oral contraceptives

Triphasic—gestodene		*Triphasic—levonorgestrel*	
Dose	*Days*	*Dose*	*Days*
50 μg gestodene-30 μg ethinylestradiol	1-6	50 μg levonorgestrel-30 μg ethinylestradiol	1-6
70 μg gestodene-40 μg ethinylestradiol	7-11	75 μg levonorgestrel-40 μg ethinylestradiol	7-11
100 μg gestodene-30 μg ethinylestradiol	12-21	125 μg levonorgestrel-30 μg ethinylestradiol	12-21

Table II. Serum hormones and SHBG before and during treatment

Parameter	*Control cycle, Luteal phase*	*EE + LNG*		*EE + GES*	
		Cycle 3	*Cycle 6*	*Cycle 3*	*Cycle 6*
Progesterone (nmol/L)	39.8 ± 3.2	4.86 ± 1.84	2.88 ± 0.48	2.99 ± 0.34	2.49 ± 0.48
Estradiol (nmol/L)	0.54 ± 0.03	0.12 ± 0.05	0.11 ± 0.04	0.06 ± 0.00	0.05 ± 0.00
LH (IU/L)	8.38 ± 1.04	8.04 ± 2.09	7.04 ± 2.00	3.86 ± 0.42	3.95 ± 0.68
FSH (IU/L)	2.87 ± 0.22	3.22 ± 0.61	2.86 ± 0.48	1.89 ± 0.19	2.04 ± 0.23
SHBG (nmol/L)	52.5 ± 3.0	95.0* ± 6.1	98.0* ± 7.8	145* ± 12.5	152* ± 14.4
n	33	17	16	16	13

Values are mean ± SEM
LH, Luteinizing hormone; *FSH*, follicle-stimulating hormone.
*$p < 0.001$ (treatment versus controls).

were measured by precipitation and electroimmunoassay.[4-6] Antithrombin III and factor VII were measured by function, and fibrinogen was measured by coagulometric.[7]

Results are presented as mean ± SEM and are statistically evaluated by analysis of variance, followed by Duncan's test for multiple comparisons, $p < 0.05$ was considered significant.

Results

Clinical. Of the 33 women who entered the study, all completed three treatment cycles and 29 completed six cycles.

Both OC preparations gave good cycle control with a bleeding duration of 2 to 7 days. No woman reported withdrawal bleeding, but two women in each group had completely irregular bleeding. Three women in the GES group and two in the LNG group had an episode of breakthrough bleeding or spotting.

Three women in the LNG group and two in the GES group reported an increase in body weight of 2 to 3 kg.

Laboratory. Table II presents the serum levels of the endogenic hormone response and SHBG. Progesterone was depressed below 9 nmol/L in both treatment groups. Serum levels of estradiol, luteinizing hormone, and follicle-stimulating hormone were depressed to or below early follicular phase levels; they were more pronounced during treatment with GES than with LNG. Serum levels of SHBG, the main carrier protein of GES and LNG,[8] increased twofold during treatment with EE + LNG and threefold during treatment with EE + GES ($p < 0.001$).

Individual serum levels of progestogens were measured. The GES concentration varied from 6.4 to 30.8 nmol/L in the third cycle and increased to values of 8.2 to 27.9 nmol/L in the sixth treatment cycle ($p < 0.05$). In the LNG group measured LNG concentrations were unchanged between the third and sixth cycles of treatment, with a variation from 6.6 to 12.6 and 4.4 to 16.0 nmol/L, respectively. After correction for variation in SHBG binding, the levels of the two hormones varied less. GES ranged from 5.0 to 15.0 and LNG ranged from 5.4 to 14.9 nmol/L.

As shown in Table III, high-density lipoprotein$_2$ (HDL_2) cholesterol decreased in the group receiving LNG ($p < 0.05$), with 36% and 19% after 3 and 6 treatment cycles. HDL_2 cholesterol was unchanged in GES-treated women. Apolipoprotein A_1 increased significantly during GES treatment ($p < 0.01$). The increase was greater after six treatment cycles. Serum levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol and HDL_3 cholesterol, and apolipoprotein B were unaffected during both treatments.

The coagulation parameters, which showed changes during OC treatment, are shown in Table IV. Antithrombin III decreased in the GES group after 6 months ($p < 0.05$). No changes were seen in women

Table III. Lipids and lipoproteins before and during treatment

Parameter	Control cycle, Luteal phase	EE + LNG		EE + GES	
		Cycle 3	Cycle 6	Cycle 3	Cycle 6
HDL_2 cholesterol (mmol/L)	0.42 ± 0.06	0.27* ± 0.04	0.34* ± 0.06	0.50 ± 0.05	0.39 ± 0.04
Apolipoprotein Al (gm/L)	1.19 ± 0.03	1.28 ± 0.04	1.24 ± 0.03	1.37* ± 0.06	1.42* ± 0.04
n	33	17	16	16	13

Values are mean ± SEM.
*$p < 0.01$ (treatment versus control).

Table IV. Coagulation parameters before and during treatment

Parameter	Control cycle, Luteal phase	EE + LNG		EE + GES	
		Cycle 3	Cycle 6	Cycle 3	Cycle 6
Antitrobin III (%)	107.5 ± 1.8	106.2 ± 3.7	103.8 ± 2.6	104.8 ± 2.9	96.2* ± 3.2
Factor VII (%)	98.1 ± 4.9	131.5* ± 12.8	147.1* ± 9.7	145.8* ± 14.9	168.0* ± 19.0
n	33	17	16	16	13

Values are mean ± SEM.
*$p < 0.01$ (treatment versus control).

receiving LNG. Factor VII was elevated in both groups ($p < 0.01$), with a greater increase in the GES group. No changes in fibrinogen were seen.

Comment

Both preparations had good and similar contraceptive effects and cycle control. The incidence of irregular bleeding and spotting was low in both groups. This could be because of similar serum levels of progestogens found in both groups.

Both OC inhibited ovulation effectively as determined from the low progesterone levels. Despite the lower dose of GES compared with LNG, serum follicle-stimulating hormone and estradiol were lower in the GES group, which indicated that GES has a stronger progestogenic effect than did LNG. This is consistent with previous reports.[9] The rise in SHBG caused by EE appeared to be less counteracted by GES than by LNG. The two progestogens are strongly bound to SHBG (40% to 50%),[10] and this reduces the metabolic clearance rate and thereby raises the concentrations. The considerable interindividual variation in steady-state concentration reflected similar variations in SHBG levels, and therefore less variability in the biologically available fractions of LNG and GES was observed.

Changes in lipoprotein levels are associated with the incidence of cardiovascular disease. High levels of low-density lipoprotein and low levels of HDL cholesterol increase the risk of cardiovascular disease. The subfraction of HDL cholesterol, HDL_2 cholesterol, has a protective ability,[11, 12] along with the main carrier protein of HDL, apolipoprotein A_1. The finding that HDL_2 cholesterol was unchanged and that apolipoprotein A_1 increased in the GES group whereas HDL_2 cholesterol decreased in the LNG group speaks in favor of GES in respect to cardiovascular disease.

In general estrogens increase HDL cholesterol levels, and this effect is counteracted by progestogens, depending on their androgenicity.[13] Our study showed that GES had less androgen activity compared with LNG as reflected in SHBG levels.[14]

The natural anticoagulant, antithrombin III, decreased in the GES group. However, some authors emphasize that only significant changes (59%) are of any clinical relevance.[2] Factor VII of the "extrinsic pathway" increased in both groups, whereas fibrinogen was unchanged. The changes in the hemostatic system were small but were most pronounced in the GES group. Whether minor changes in coagulation parameters are of importance from a clinical point of view is doubtful.[15]

In conclusion we found that GES combined with EE in low-dose triphasic preparation, inhibited ovulation. Serum levels of GES showed greater variation than did LNG, but the unbound bioavailable fraction varied much less because of binding to SHBG, of which the concentration increased substantially. GES seemed to have a more favorable influence on lipid metabolism than did LNG, probably because of lower androgenicity, and GES affected coagulation factors slightly more than LNG, but the clinical importance is not obvious at the present time.

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Effects of ethinyl estradiol combined with desogestrel and cyproterone acetate on glucose tolerance and insulin response to an oral glucose load: A one-year randomized, prospective, comparative trial

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To investigate the effects of two slightly estrogen-dominant, monophasic, low-dose oral contraceptives on carbohydrate metabolism, 40 healthy young women were randomly allocated to receive either 30 μg of ethinyl estradiol + 150 μg of desogestrel, a 19-nortestosterone–derived progestin (Marvelon; $n = 21$) or 35 μg of ethinyl estradiol + 2 mg of cyproterone acetate, a 17-acetoxyprogesterone derivative (Diane-35; $n = (19)$ for a prospective observation period of 1 year. At baseline, 6, and 12 months, blood glucose, plasma insulin, and plasma C-peptide levels were measured during an oral glucose tolerance test. Although the changes were absent (Marvelon) or minimal (Diane-35) at 6 months, both groups had a slight increase in blood glucose levels at 12 months; overall glucose tolerance remaining, however, within the normal range. Plasma insulin levels remained unchanged in the Diane-35 group, which suggested increased insulin resistance, but were significantly decreased in the Marvelon group despite significant rises in plasma C–peptide levels. Comparison of plasma C-peptide and insulin changes suggests enhanced pancreatic insulin secretion and increased hepatic insulin metabolism with both Marvelon and Diane-35. (Am J Obstet Gynecol 1990;163:378-81.)

Key words: Carbohydrate metabolism, glucose tolerance, insulin metabolism, insulin secretion, oral contraceptives

Many studies have investigated the extent of the potential alterations in carbohydrate metabolism caused by different steroid types and dosages in combined oral contraceptives. It is now commonly accepted that low doses of estrogens, including ethinyl estradiol, have only very limited effects on glucose tolerance; thus the progestin compound appears to play the most important role.[1]

The aim of this study was to compare the potential effects on carbohydrate metabolism of two slightly estrogen-dominant monophasic oral contraceptive containing low-dose ethinyl estradiol plus either desogestrel (Marvelon) or cyproterone acetate (Diane-35). For that purpose, we designed a 1-year randomized, prospective study in normal women. In addition to glucose tolerance, we measured not only peripheral plasma insulin levels but also plasma C-peptide concentrations to assess pancreatic insulin secretion and insulin metabolism.

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Subjects

The characteristics of the subjects investigated were quite comparable in both groups treated with either Marvelon or Diane (Table I). Forty healthy Belgian young women about 20 to 30 years of age, most of whom were medical students and nurses recruited from our University Hospital, participated. They had either never used oral contraceptives previously or discontinued use of oral contraceptives for at least 8 weeks before the study. In particular, none had a family history of diabetes, all were within 15% of their ideal body weight, and were nonsmokers. No differences in clinical characteristics, alcohol drinking habits, or physical exercise were demonstrable between the groups. They had none of the usual contraindications to oral contraceptive use. All subjects gave their free and informed consent, and the study was approved by the Ethical Committee for Human Investigations of the University of Liège.

Treatment

The subjects were randomly allocated for 12 months to receive either Marvelon ($n = 21$), 30 μg of ethinyl estradiol + 150 μg of desogestrel, a 19-nortestosterone (gonane) derivative with slight androgenic/antiestrogenic properties,[2] or Diane-35 ($n = 19$), 35 μg of eth-

Table I. Characteristics of subjects investigated (mean ± SEM)

	Age (yr)	*Height (cm)*	*Weight (kg)*	*Body mass index (kg/m^2)*
Diane-35 (n = 19)	25.1 ± 0.9	165.5 ± 1.3	57.6 ± 1.5	21.0 ± 0.5
Marvelon (n = 21)	23.8 ± 0.7	164.0 ± 1.2	54.4 ± 1.5	20.0 ± 0.4
	NS	NS	NS	NS

Table II. Changes in blood glucose, plasma insulin, plasma C-peptide, and C-peptide/immunoreactive insulin molar ratio under Diane-35 (n = 19); results correspond to changes at 6 and 12 months from 0 month values (expressed in percent)

	T6 vs T0		*T12 vs T0*	
	Fasting values	*$AUC_{0\text{-}180\ min}$*	*Fasting values*	*$AUC_{0\text{-}180\ min}$*
Blood glucose	−1.6% (NS)	+14.7% ($p < 0.10$)	+12.5% ($p < 0.005$)	+18.4% ($p < 0.005$)
Plasma insulin	+10.0% (NS)	+23.8% (NS)	+0.3% (NS)	+8.4% (NS)
Plasma C-peptide	+14.3% ($p < 0.01$)	+29.9% ($p < 0.02$)	+26.5% ($p < 0.005$)	+35.5% ($p < 0.005$)
C-peptide/immunoreactive insulin	+7.9% (NS)	+23.6% ($p < 0.10$)	+15.8% (NS)	+45.4% ($p < 0.05$)

T6, 6 months; *T0*, baseline; *T12*, 12 months; *AUC*, area under the curve.

inyl estradiol + 2 mg of cyproterone acetate, a 17-acetoxyprogesterone progestin with antiandrogenic activity.[3]

Experimental procedure

Carbohydrate metabolism was assessed by means of an oral glucose tolerance test (75 gm of glucose dissolved in 300 ml of water). This oral glucose tolerance test was performed after an overnight fast, during the last 7 days before presumed menstruation in a spontaneous cycle (baseline) and within the last 5 days of pill intake during the sixth and twelfth months of oral contraceptive use in each subject. To avoid potential circannual changes in endogenous insulin secretion in response to glucose loading, the 40 subjects were introduced into the study at different time intervals over a 9-month period.

Blood samples. Blood samples were collected through a flexible catheter inserted into a superficial forearm vein before and every 30 minutes for 3 hours after the ingestion of glucose. Blood glucose was determined by the hexokinase method, plasma immunoreactive insulin by a method derived from the C-method of Hales and Randle,[4] and plasma C-peptide by the radioimmunoassay method of Heding.[5] Samples for immunoreactive insulin and C-peptide were kept frozen until the end of the study period for each subject and run in duplicate in the same assay procedures, thereby minimizing interassay variability and multiple thawing of samples.

Calculations and statistical evaluation. For each group, the means and standard errors of the means for all parameters were calculated at each time of measurement. The areas under the curves from 0 to 180 minutes were then calculated by the trapezoidal method. Results are expressed as changes (±%) at six and 12 months from values obtained at baseline. The statistical evaluation was performed according to the Student t test for paired values.

Results

Diane-35 (Table II). Initial fasting blood glucose values were normal in all persons tested; however, a slight but significant increase was recorded at 12 months. Blood glucose levels recorded during the pretreatment oral glucose tolerance test (baseline) were within the normal range. During treatment, a trend to a moderate increase in area under the curve blood glucose was already observed at 6 months; this difference was significant at 12 months of therapy. However, no value of blood glucose level attained a pathological level, indicating impaired glucose tolerance. At 6 months, a tendency to increased fasting immunoreactive insulin values and area under the curve immunoreactive insulin was observed; however, the differences did not reach statistical significance mostly because of the interindividual fluctuations in plasma immunoreactive insulin levels and almost disappeared after 12 months of therapy. In contrast, fasting plasma C-peptide levels and area under the curve C-peptide were significantly increased throughout the treatment period, at 6 months, and even more at 12 months. Thus the C-peptide/immunoreactive insulin molar ratio measured in the fasting state tended to be slightly increased under Diane-

Table III. Changes in blood glucose, plasma insulin, plasma C-peptide, and C-peptide/immunoreactive insulin molar ratio under Marvelon ($n = 21$); results correspond to changes at 6 and 12 months from 0 month values (expressed in percent)

	T6 vs T0		*T12 vs T0*	
	Fasting values	$AUC_{0\text{-}180\ min}$	*Fasting values*	$AUC_{0\text{-}180\ min}$
Blood glucose	+1.6% (NS)	+7.4% (NS)	+5.7% (NS)	+13.9% ($p < 0.005$)
Plasma insulin	−9.1% (NS)	+0.7% (NS)	−27.3% ($p < 0.10$)	−21.1% ($p < 0.005$)
Plasma C-peptide	+1.9% (NS)	+4.6% (NS)	+13.0% ($p < 0.10$)	+19.3% ($p < 0.01$)
C-peptide/immunoreactive insulin	+36.4% (NS)	+12.4% (NS)	+86.9% ($p < 0.005$)	+54.2% ($p < 0.001$)

T6, 6 months; *T0*, baseline; *T12*, 12 months; *AUC*, area under the curve.

35; this increase was more marked when considering the molar ratio area under the curve C-peptide/area under the curve immunoreactive insulin and became highly significant after 12 months of therapy.

Marvelon (Table III). Fasting blood glucose levels and glucose tolerance assessed during the pretreatment oral glucose tolerance test (baseline) were strictly within the normal range. At 6 months, no significant differences were observed for blood glucose, plasma immunoreactive insulin, and C-peptide levels either in the fasting state or during the oral glucose tolerance test. At 12 months, a discrete, nonsignificant increase in fasting blood glucose levels was recorded, with a significant increase in the mean area under the curve blood glucose. However, here again, no subject met the criteria of impaired glucose tolerance. A tendency toward decreased fasting plasma immunoreactive insulin levels was observed with a significant reduction of the insulin response to the glucose load, as reflected by the lower area under the curve immunoreactive insulin. In contrast, fasting plasma C-peptide levels tended to increase, and area under the curve C-peptide showed a significant enhancement of insulin secretion. Thus although unchanged at 6 months, the C-peptide/immunoreactive insulin molar ratio, which was calculated in both basal and postglucose conditions, significantly increased at 12 months.

Comment

It has been known for a long time that oral contraceptive use may increase the risk of developing altered glucose tolerance[1]; impairment of glucose tolerance and hyperinsulinism, which indicates a state of insulin resistance, are involved in the occurrence of cardiovascular disease, hypertension, and non-insulin-dependent diabetes mellitus.[6,7]

Previous studies have shown that progestogens derived from 17-hydroxyprogesterone have a lower potential for impairing glucose tolerance and increasing insulin resistance than do the more potent 19-nortestosterone derivatives.[1]

In contrast, our study with Diane-35, containing a 17-acetoxyprogesterone derivative, clearly demonstrated a slight deterioration in glucose tolerance, which was significant after 12 months of use; however, no blood glucose value reached the degree of impaired glucose tolerance. This increase in blood glucose levels occurred without any decrease in plasma immunoreactive insulin levels; this suggests a mechanism of insulin resistance that is still poorly understood and could involve reduced levels of hepatic insulin receptors as well as postreceptor changes in intracellular glucose metabolism.[8] According to this latter hypothesis, a recent in vivo study with the euglycemic clamp technique has shown that oral contraceptive administration (30 μg of ethinyl estradiol + 150 μg of levonorgestrel) induced a significant reduction of the insulin-induced glucose disposal, suggesting peripheral (muscular) tissue insulin resistance.[9] Although plasma immunoreactive insulin levels remained almost unchanged throughout our study, we observed a highly significant increase in plasma C-peptide levels, suggesting increased pancreatic insulin secretion but enhanced insulin metabolism.

With Marvelon, two 6-month studies have reported a slight deterioration in glucose tolerance (increase in blood glucose levels) but with conflictual results on insulin response. The first study showed a statistically significant increase in plasma immunoreactive insulin levels, which suggests the development of insulin resistance,[10] whereas our study[11] demonstrated a decrease in insulin response. Our first interpretation was that this difference could be attributed to circannual changes in glucose-insulin homeostasis, as observed by Reinberg et al.[12] Accordingly we modified our subsequent protocol to avoid this interference, and here again we confirm the occurrence of a slight but significant decrease in plasma immunoreactive insulin levels, which was even more pronounced after 12 months of treatment. Because we recorded simultaneously an increase in plasma C-peptide levels, we can conclude that insulin secretion is stimulated, but that at the same time,

the metabolic clearance rate of insulin is enhanced. The interference of oral contraceptive agents with the liver metabolism is of common knowledge, and more than 50% of insulin is extracted by the liver. Thus we can suspect a possible interference at this hepatic level. Moreover, we have recently reported that the classic potentiation by obesity of the peripheral hyperinsulinism observed during an oral glucose tolerance test almost disappears during the last trimester of pregnancy.[13]

It would be interesting to carry out protocols studying carefully the metabolic clearance rate of insulin during oral contraceptive treatment. To the best of our knowledge, only one study has recently demonstrated that a combination oral contraceptive containing 30 μg of ethinyl estradiol + 150 μg of levonorgestrel did not significantly affect the metabolic clearance rate of insulin.[9] However, that study was performed after only 3 and 6 months of treatment, namely, a duration after which we did not find any significant changes in the C-peptide/immunoreactive insulin molar ratio in our study. Therefore more prolonged studies are needed before any definite conclusions can be drawn on this matter.

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Effects of oral contraceptives on carbohydrate and lipid metabolisms in a healthy population: The Telecom Study

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In a cross-sectional study that aimed to identify risk factors for diabetes, 1290 consecutive, healthy, nonpregnant women of child-bearing age were examined in a center for preventive medicine. An in-depth interview about menses, use of oral contraceptives, and menopause was performed. Plasma glucose at fasting and 2 hours after a 75 gm glucose load, glycated hemoglobin A_{1c}, fasting plasma insulin, total plasma cholesterol, and triglycerides were measured. Compared with nonusers taking no progestogens, oral contraceptive users (n = 431;33.4%) were younger ($p < 0.001$) and leaner ($p < 0.001$). After adjustment for age and body mass index, oral contraceptive users had higher 2-hour plasma glucose ($p < 0.001$), higher fasting plasma insulin ($p < 0.01$), and higher triglycerides levels ($p < 0.01$). Fasting plasma glucose, glycated hemoglobin A_{1c}, and total cholesterol did not significantly differ between the two groups. In relation to dosage and types of steroid components, few differences have been found between high-dose and low-dose oral contraceptives or according to the estrogen-progestogen balance of the preparations. Use of oral contraceptives appears to induce an increase of insulin-resistance markers, which have recently been cited as risk factors for ischemic vascular diseases. These markers should be carefully monitored in oral contraceptive users. (Am J Obstet Gynecol 1990;163:382-7.)

Key words: Oral contraceptives, high-dose/low-dose oral contraceptives, estrogen/progestogen balance, insulin resistance

Oral contraceptives are the most popular reversible method of contraception in the United States[1] and probably in all developed countries. Their low rate of failure, ranked second behind sterilization,[2] low cost, and acceptability will probably help keep consumption of oral contraceptives very high in the next decade worldwide. Thus there is a need to evaluate very carefully their side effects. Despite criticisms, which are mainly addressed at the observational nature of study designs used to investigate the relationship between oral contraceptives and cardiovascular diseases,[3] it is currently admitted that most of the epidemiologic surveys have indicated a link between oral contraceptive use and adverse cardiovascular events.[4-8] Oral contraceptives seem to generate these effects through deleterious changes in the coagulation process and in carbohydrate and lipid metabolisms.[9, 10] To reduce cardiovascular risk, a large-scale move toward preparations containing low doses of estrogens was initiated in the early 1970s, followed a few years later by efforts to minimize the dose of progestogens.[11, 12] Consequences of these changes in oral contraceptives prescription habits on carbohydrate and lipid metabolisms have been poorly evaluated as the ideal design—a prospective, comparative, randomized study of each new oral contraceptive[9] is difficult to realize because of obvious ethical and practical reasons. Moreover, the few surveys designed to address this issue have often been conducted on small samples and have led to contradictory conclusions.[13-21] Therefore this article assesses the influence of oral contraceptives on metabolic parameters in a large, healthy, female population and makes a comparison between oral contraceptive users and nonusers, and among users, according to estrogen dosage and estrogen/progestogen balance of the preparations.

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Subjects and methods

From April 1985 to October 1987, 1290 consecutive, healthy women of child-bearing age, who voluntarily attended a center for preventive medicine, were examined in a cross-sectional study. Women who were pregnant, who had a self-reported history of diabetes, who were treated by progestogens alone, or who had hemoglobinopathies, were excluded. The subjects were "France-Telecom" employees working in the Paris area who are offered a medical check-up, free of charge,

Table I. Description of the population

Characteristics	*No hormonal treatment (n = 859)*	*OC (n = 431)*	*p value*
Ethnic origin (%)			
White	85.9	88.7	
Black	13.4	10.8	NS
Asian	0.7	0.5	
Age (yr)	38.5 ± 0.3	29.5 ± 0.3	<0.001
Smokers (%)	23.7	34.2	0.72*
Family history of diabetes (%)	14.6	8.4	0.11*
Body mass index (kg/m²)	23.0 ± 0.1	21.5 ± 0.1	<0.001
Systolic blood pressure (mm Hg)†	118.4 ± 0.4	120.1 ± 0.7	<0.05
Diastolic blood pressure (mm Hg)†	68.3 ± 0.4	70.2 ± 0.6	0.01
GGT (U/L)†‡	9.5 (9.1-9.8)	11.2 (10.6-11.8)	<0.001
SHBG (nmol/L)†‡	36.5 (34.7-38.4)	56.7 (52.3-61.4)	<0.001

Results show percentage or mean ± SEM as appropriate.

GGT, γ-Glutamyltransferase; *SHBG*, sex hormone–binding globulin.

**p* Value calculated after adjustment for age.

†Values adjusted for age and body mass index (calculated for age = 35 years and body mass index = 22.5 kg/m²).

‡Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

every 5 years for those under 40 years and every 2 years for those over 40 years.

A self-questionnaire, which was filled out at home, inquired about gynecologic and obstetric history, present oral contraceptive use with the brand name if any, regularity of menstrual cycle, and the first day of the last period. During the consultation, a secretary reviewed carefully all these data with the client and gave her a letter to be returned when her next menses began; 80% responded and indicated the date of the following menses.

Height, weight, and blood pressure were recorded at physical examination. The Quetelet index [weight(kg)/height(m)²] was used as a measure of body mass index. Fasting plasma glucose, plasma insulin (22), total cholesterol, triglycerides, and glycated hemoglobin A_{1c}[23] were measured and plasma glucose was also measured 2 hours after a 75 gm glucose load (2-hour plasma glucose).

Table I describes the study population and compares each nonmetabolic parameter between oral contraceptive users and nonusers. The sample consisted of around 87% whites and 12% blacks, mainly natives from the West Indies. Oral contraceptive users were significantly younger and leaner (Table I). After adjustment for age and body mass index, systolic and diastolic blood pressures were significantly higher in oral contraceptive users who also had significantly higher level of γ-glutamyltransferase and sex hormone–binding globulin (Table I).

Regarding metabolic parameters, comparisons have been made between oral contraceptive users and nonusers in a first step. Among users, subdivisions were then made according to dosage and types of steroid components. Thus by crossing estrogen content (high-dose/low-dose) with hormonal balance (estrogen/progestogen dominance), four subgroups of oral contraceptives have been identified (Table II), in which dosage of ethinyl estradiol, progestogen content, and number of users have been indicated for each oral contraceptive.

This classification of oral contraceptives led us to perform four comparisons in a second step: between high-dose and low-dose oral contraceptive users inside each hormone-dominance group and between estrogen-dominant and progestogen-dominant oral contraceptive users inside each estrogen-dose group. Statistical analysis used programs accessible through SAS[24] on a VAX 8530. The χ^2 tests and analysis of variance have been performed after logarithmic transformation when needed. When a significant difference has been observed for age or/and body mass index, comparisons for metabolic parameters have been adjusted for age or/and body mass index. For quantitative variables, the values reported are mean ± SEM or the mean followed by the 95% confidence interval for the mean when logarithmic transformation has been needed.

Results

Compared with the 859 oral contraceptive nonusers, the 431 oral contraceptive users were not significantly different for hemoglobin A_{1c}, fasting plasma glucose, and total cholesterol concentrations (Table III), but they had significantly higher 2-hour plasma glucose, higher fasting plasma insulin, and higher triglyceride levels as shown in Table III.

Within both the estrogen-dominant (Table IV) and the progestogen-dominant (Table V) oral contraceptive users, no significant difference has been observed according to the estrogen dose of oral contraceptives.

Table II. Oral contraceptives used

	Brand name	*Progestogen content (mg)*		*n*
High dose (50 γ ethinyl estradiol)				
Estrogen dominance	Diane	Cyproterone acetate	2	20
	Ovanon	Lynestrenol	1.8*	7
	Physiostat	Lynestrenol	0.7*	1
	Milli-Anovlar	Norethisterone acetate	1	1
	Progylut	Norethisterone acetate	1*	1
Progestogen dominance	Stediril	DL. Norgestrel	0.5	45
	Planor	Norgestrienone	2	6
	Gynophase	Norethisterone acetate	1.5*	5
	Gynovlane	Norethisterone acetate	2	5
	Anovlar	Norethisterone acetate	4	1
Low dose (<40 γ ethinyl estradiol)				
Estrogen dominance	Varnoline	Desogestrel	0.15	34
	Triella	Norethisterone	0.75*	28
	Trinordiol	Levonorgestrel	0.09*	8
	Ovamezzo	Lynestrenol	0.75	2
	Normapause	Norethisterone	0.25*	1
Progestogen dominance	Adepal	Levonorgestrel	0.18*	166
	Minidril	Levonorgestrel	0.15	52
	Miniphase	Norethisterone acetate	1.5*	37
	Trentovlane	Norethisterone acetate	1	6
	Ortho-Novum	Norethisterone	1	4

*Mean progestogen content per tablet for sequential and phasic oral contraceptives.

Table III. Carbohydrate and lipid metabolisms according to use of oral contraceptives

Parameter	*No hormonal treatment (n = 859)*	*Oral contraceptives (n = 431)*	*p value*
Hemoglobin A_{1c} (% total hemoglobin)	4.95 ± 0.02	4.89 ± 0.03	0.17
Fasting plasma glucose (mg/dl)	86.7 ± 0.3	85.9 ± 0.4	0.11
2 hr plasma glucose (mg/dl)	99 ± 1	108 ± 1	<0.001
Fasting plasma insulin (μU/ml)*	6.7 (6.5-6.9)	7.3 (7.0-7.6)	<0.01
Total plasma cholesterol (mg/dl)	214 ± 1	212 ± 2	0.52
Plasma triglycerides (mg/dl)*	59 (57-61)	74 (71-77)	<0.01

All values (mean ± SEM) are adjusted for age and body mass index (calculated for age = 35 years and body mass index = 22.5 kg/m²).

*Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Table IV. Influence of estrogen dose in estrogen-dominant oral contraceptive users

Parameter	*Low dose (n = 73)*	*High dose (n = 39)*	*p value*
Age (yr)	28.6 ± 0.7	31.0 ± 0.9	0.05
Body mass index (kg/m²)	22.1 ± 0.3	21.9 ± 0.5	0.70
Hemoglobin A_{1c} (% total hemoglobin)*	4.77 ± 0.06	4.71 ± 0.10	0.64
Fasting plasma glucose (mg/dl)*	84.3 ± 0.7	82.6 ± 1.1	0.20
2 hr plasma glucose (mg/dl)*	103 ± 3	98 ± 5	0.44
Fasting plasma insulin (μU/ml)*†	7.7 (7.0-8.4)	7.5 (6.5-8.6)	0.72
Total plasma cholesterol (mg/dl)*	209 ± 4	206 ± 6	0.70
Plasma triglycerides (mg/dl)*†	78 (72-86)	77 (68-88)	0.83

*Value adjusted for age (calculated for age = 29.3 years).

†Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Among high-dose users, the estrogen-progestogen balance did not influence metabolic parameters (Table VI). On the contrary, when low-dose oral contraceptive users were considered, significant differences were found according to the estrogen-progestogen balance of the preparations (Table VII): users of progestogen-dominant, low-dose oral contraceptives were leaner ($p = 0.02$); after adjustment for body mass index, they had a marginally significant higher hemoglobin A_{1c} level (4.90% ± 0.03% vs 4.77% ± 0.07%; $p = 0.06$), with slighlty higher but nonsignificantly different plasma glucose values; their triglyceride level was significantly lower (71 mg/dl with 95% confidence interval = 68 to 74 mg/dl vs 78 mg/dl with 95% confidence

Table V. Influence of estrogen dose in progestogen-dominant oral contraceptive users

Parameter	*Low dose (n = 265)*	*High dose (n = 62)*	*p value*
Age (yr)	29.3 ± 0.4	30.5 ± 0.8	0.18
Body mass index (kg/m^2)	21.4 ± 0.1	21.4 ± 0.3	0.86
Hemoglobin A_{1c} (% total hemoglobin)	4.90 ± 0.03	4.82 ± 0.07	0.34
Fasting plasma glucose (mg/dl)	83.9 ± 0.4	83.4 ± 0.7	0.60
2 hr plasma glucose (mg/dl)	104 ± 1	109 ± 4	0.19
Fasting plasma insulin (μU/ml)*	7.3 (7.0-7.6)	6.8 (6.3-7.3)	0.12
Total plasma cholesterol (mg/dl)	208 ± 2	210 ± 4	0.61
Plasma triglycerides (mg/dl)*	71 (68-74)	71 (65-78)	0.89

*Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Table VI. Influence of estrogen-progestogen balance in high-dose oral contraceptive users

Parameter	*Estrogen dominant (n = 30)*	*Progestogen dominant (n = 62)*	*p value*
Age (yr)	31.0 ± 0.9	30.5 ± 0.8	0.68
Body mass index (kg/m^2)	21.9 ± 0.5	21.4 ± 0.3	0.40
Hemoglobin A_{1c} (% total hemoglobin)	4.75 ± 0.09	4.82 ± 0.07	0.48
Fasting plasma glucose (mg/dl)	83.7 ± 1.3	83.4 ± 0.7	0.82
2 hr plasma glucose (mg/dl)	99 ± 5	109 ± 4	0.10
Fasting plasma insulin (μU/ml)*	7.4 (6.6-8.3)	6.8 (6.3-7.3)	0.19
Total plasma cholesterol (mg/dl)	207 ± 5	210 ± 4	0.66
Plasma triglycerides (mg/dl)*	77 (68-88)	71 (65-78)	0.31

*Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

interval = 72 to 85 mg/dl; $p = 0.03$) and the fasting plasma insulin slighlty but nonsignificantly decreased. No difference was observed for total cholesterol (Table VII).

Table VII. Influence of estrogen-progestogen balance in low dose oral contraceptive users

Parameter	*Estrogen dominant (n = 73)*	*Progestogen dominant (n = 265)*	*p value*
Age (yr)	28.6 ± 0.7	29.3 ± 0.4	0.40
Body mass index (kg/m^2)	22.1 ± 0.3	21.4 ± 0.1	0.02
Hemoglobin A_{1c} (% total hemoglobin)*	4.77 ± 0.07	4.90 ± 0.03	0.06
Fasting plasma glucose (mg/dl)*	83.6 ± 0.8	84.1 ± 0.4	0.43
2 hr plasma glucose (mg/dl)*	102 ± 3	104 ± 1	0.46
Fasting plasma insulin (μU/ml)*†	7.6 (7.1-8.3)	7.3 (7.0-7.6)	0.52
Total plasma cholesterol (mg/dl)*	208 ± 2	209 ± 4	0.99
Plasma triglycerides (mg/dl)*†	78 (72-85)	71 (68-74)	0.03

*Values adjusted for body mass index (calculated for body mass index = 21.8 kg/m^2).

†Geometric mean with 95% confidence interval of mean in brackets when logarithmic transformation has been needed.

Comment

Because recruitment was occupation based and consisted of volunteers, the sample of the study cannot be considered as representative of the French female population of child-bearing age: compared with a representative French sample of the same age,[25] a higher percentage of oral contraceptive users was found in our group (33.4% vs 28%; $p < 0.001$). This discrepancy can be explained by a difference in socioeconomic class, which was probably higher in our sample because subjects worked in a high-tech organization in the Paris area. It could also be from the lag time between the two surveys: oral contraceptive use probably increased in France between 1978 and 1985. Nevertheless, this lack of representativeness has probably no or little effect on the relationship observed between oral contraceptive use and metabolic abnormalities observed in our study. It is more important to emphasize the observational nature of this study: in daily medical practice, contraceptive method is not randomly allocated, but the most appropriate tool of contraception is proposed to each individual according to a set of characteristics—age, weight, personal gynecologic and obstetric history, family history of metabolic diseases, blood pressure, plasma glucose, and cholesterol values. This statement can explain a large part of the differences observed in age and probably also in body mass index between oral contraceptive users and nonusers. Adjustments for age and for body mass index were made to reduce discrepancies between the two groups.

Elevated values of 2-hour plasma glucose, fasting plasma insulin, and triglycerides we have observed in oral contraceptive users confirm previous published data.[9, 10, 15, 26, 27] Even if the cause of the increased incidence of both venous and arterial cardiovascular diseases in users of oral contraceptives appears to be thrombosis and not atherogenesis,[10] prospective studies have underlined the role of early markers of insulin resistance[28] as cardiovascular risk factors.[29, 30] Thus these markers should be carefully monitored in oral contraceptive users, at least for long-term use. On the contrary, no difference has been observed between oral contraceptive users and nonusers concerning fasting plasma glucose and hemoglobin A_{1c}—a cumulative es-

timate of the mean blood glucose concentration over the preceding 2 to 3 months,[31] more closely linked to fasting plasma glucose than to 2-hour plasma glucose.[32] It indicates the minimal or absent influence of oral contraceptives on basal glucose metabolism as previously reported.[27] As to total cholesterol, which did not differ according to oral contraceptive use, few conclusions can be drawn because cholesterol subfractions have not been measured.

The change in oral contraceptive prescriptions to low-dose preparations is probably reflected by the younger age of oral contraceptive users. The aim to reduce the metabolic disturbances of oral contraceptives appears not to have been reached according to our data. Once again, the observational nature of this study can explain such a result because a selection bias could interfer. A lack of power could also be considered an explanation. We must also be reminded that the relative safety of low-dose oral contraceptives with regard to cardiovascular reactions[11] has been argued at least concerning mortality from thromboembolic disease and frequency of arterial complications.[33] Thus the metabolic (and may be also the hemostatic) benefit of the reduction of estrogen content could indeed be not as important as expected.

The metabolic influence of the estrogen/progestogen balance appears negligible within the high-dose oral contraceptive group. Among low-dose oral contraceptive users, carbohydrate metabolism does not significantly differ according to the hormone balance, as previously reported.[21] The difference in plasma triglycerides, which are significantly lower in the progestogen-dominant group, must be considered cautiously, because many comparisons have been performed between all subgroups and the one significant difference ($p = 0.03$) could have been found only by chance. Such a decrease in triglycerides level with higher doses of progestogens seems contradictory to usual findings.[9]

This cross-sectional study underlines the metabolic alterations in oral contraceptive use, namely, an increase in insulin-resistance markers, which seems predictive of permanent diabetes[34] and could be involved in the atherogenic process.[29, 30] Monitoring of these indexes should be systematically performed on oral contraceptive users, mainly on women at risk for diabetes (history of gestational diabetes, family history of diabetes, or obesity) and treated with oral contraceptives for a long period. The composition of oral contraceptives appears to have little influence on carbohydrate and lipid metabolisms.

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The clinical relevance of oral contraceptive pill–induced plasma lipid changes: Facts and fiction

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The changes in plasma lipids induced by the use of oral contraceptive pills have been shown in several studies to remain within normal physiologic limits. These changes are then probably without any clinical relevance because there is no evidence in the huge volume of oral contraceptive and cardiovascular literature that the use of oral contraceptives promotes or retards the development of atherosclerotic disease. What may appear to be favorable changes in the lipid profile attributed to oral contraceptive use may actually be associated with unfavorable changes in other parameters, such as the balance of clotting and fibrinolytic factors. A well-balanced, low-dose oral contraceptive formulation should alter any of the cardiovascular risk indicators as little as possible in either a supposedly positive or negative direction. (Am J Obstet Gynecol 1990;163:388-91.)

Key words: Oral contraception, pill-induced metabolic changes, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, progestogens, antiestrogenic effects

The prevailing concept regarding the role of the various lipoprotein fractions is, the "good" high-density lipoprotein cholesterol (HDL-C) transports cholesterol away from the blood vessel walls and thus protects from atherosclerotic disease. The "bad" low-density lipoprotein cholesterol does the opposite and therefore increases atherogenic risk.

In recent years, we have witnessed a plethora of published studies and reviews on oral contraceptive (OC) pill–induced changes in lipids, lipoproteins, apolipoproteins, and their ratios.[1] Some of these changes were associated with the development of atherosclerotic disease. However, these were found only in some of the epidemiologic studies among general populations. Of the actual cohort studies among women taking OCs, only the Royal College of General Practitioners' Study found a statistically significant association of OC use with cardiovascular mortality.[2] However, even so, the increased deaths in this study were not from atherosclerosis but rather were from myocardial infarction and subarachnoid hemorrhage, and these were statistically significant only in two subgroups of women: those older than 45 years and those older than 35 years old and who smoked cigarettes.[2]

What could have led to the inaccurate association between OC use and atherosclerosis? First, the term "atherogenic risk" is found in several OC publications, and somehow this may have started the association between atherogenesis, atherogenic risk, and OC use. Indeed, if there is an association between OC use and the development of atherosclerotic disease, two important questions need to be answered: (1) Is there any evidence of an OC-associated atherosclerotic risk? (2) Are there any data to show that lowering or raising HDL-C with the use of OCs promotes or retards atherosclerotic coronary or ischemic heart disease?

Therefore a review of different available studies is in order. However, before the results of these studies are evaluated, it is of critical importance to clarify some terminology.

As used in epidemiologic and cardiologic studies, the terms "coronary heart disease" or "ischemic heart disease" appear to have different meanings. In the epidemiologic OC pill literature, coronary heart disease usually refers to fatal and nonfatal myocardial infarction only.[3] When viewed from the cardiologic literature, coronary heart disease may present as either angina pectoris, myocardial infarction, or sudden cardiac death.[4] The underlying pathology of angina pectoris is most commonly atherosclerosis of the coronary arteries. On the other hand, myocardial infarction is caused in 80% to 90% of cases by coronary thromboembolic occlusion, with or without concomitant atherosclerosis.[5] In other words, the terms coronary heart disease and ischemic heart disease, as used in the epidemiologic OC literature, mainly refer to a thromboembolic event and not to an atherosclerotic event. Regarding angina pectoris, I know of no documented reports of any OC-associated angina after nearly 30 years of OC pill use.[6, 7]

Review of studies

Cohort and case-control studies in OC users. Three large epidemiologic, prospective cohort studies were initiated in 1968, a time when older, higher-dose prep-

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arations were commonly used.[2, 8, 9] As previously mentioned, only the Royal College of General Practitioners' Study found a statistically significant increase in association between OC use and cardiovascular mortality, and these deaths were from a thromboembolic event and not atherosclerosis. Thromboembolic events have indeed been the most common association attributable to OC use. In 1970 Inman et al.[10] related venous thromboembolic events to the high estrogen dose of the initial generations of OCs. In 1980 results from two other studies showed an increased risk of arterial disease (ischemic heart disease and stroke) with increasing progestogen dose.[3, 11] In addition, the Royal College of General Practitioners' Study demonstrated an inverse association between HDL-C levels, progestogen activity, and the rate of reporting arterial diseases. No arterial diseases were reported, however, with the 150 μg levonorgestrel + 30 μg ethinyl estradiol OC pill, although it was associated with a slight reduction (<10%) of HDL-C.[12]

Indeed, any cardiovascular risk from the pill may be altogether nonexistent because of the statistical and diagnostic deficiencies inherent in older epidemiologic studies.[13] In an extensive 10-year study of low-dose levonorgestrel-containing OCs in Finland,[14] comprising some 1,460,000 women-years of OC use, there was a nonsignificant association between OC use and fatal pulmonary embolism (excess risk of 1 per 1 million women/yr). Likewise, the study showed no association with cerebrovascular mortality. The use of OCs was actually shown to be protective of coronary heart disease (relative risk was 0.20; i.e., only about one fifth compared with nonusers).[14] This extensive study concluded that modern low-estrogen OCs are very safe, especially when women with risk factors and those over 40 years of age are excluded.[14]

Epidemiologic studies in general populations. Epidemiologic studies in general populations have shown a relationship between coronary heart disease and blood levels of cholesterol,[15] triglycerides,[16] and apolipoproteins.[17] Some epidemiologic studies have found an inverse relationship between HDL-C and coronary heart disease.[18] However, this finding was challenged in other more recent studies.[19] Regarding the use of OC, W. P. Castelli of the famous Framingham Study stated that heart attacks and strokes that occur among young women who take OCs are not associated with atherosclerotic narrowing of the blood vessels but rather with blood clots combined with the cigarette smoking habit.[16] Likewise, this view is supported by other investigators, such as D. R. Mishell, who studied the use of OCs in women of older reproductive age.[21]

Intervention trials. There are no trials designed to investigate the hypothesis that OC-induced lipid changes are associated with an increased or decreased incidence of cardiovascular events.[6] The only prospective controlled intervention trials with synthetic estrogens (inducing a "favorable" lipid profile) showed an association with increased cardiovascular morbidity and mortality.[20, 20A] However, these trials were performed in middle-aged and elderly men, most of whom had other predisposing factors to cardiovascular events, and therefore the results probably do not apply to healthy, young women taking OCs.[6]

Animal studies. Studies in macaque monkeys have shown that norgestrel-containing OCs protected the female animals against the development of atherosclerosis compared with control animals despite lipid changes analogous to those that occur in humans.[22] In a 31-month study, the monkeys received an atherogenic diet and the corresponding dose (15%) of an OC containing 500 μg of norgestrel and 50 μg of ethinyl estradiol. After the animals were killed, the extent of coronary arteriosclerotic lesions in the OC group was significantly less when compared with that in the males or in the untreated female controls, even though the mean total plasma cholesterol to HDL-C ratio was "unfavorably" increased.[22]

Arteriographic and necropsy findings. In various reports of myocardial infarction in 21 women taking OCs, no evidence of significant obstruction was found on arteriography in 15 cases[23-28] or at necropsy in five cases,[29-30] as well as in a Danish report on 14 necropsy cases.[31] A study among 53 women taking the OC pill and suffering from angiographically confirmed MI showed that 66% of these patients did not show any atherosclerotic changes on coronary arteriography.[32]

Comment

Thus review of the literature shows rather conflicting reports. The pill was reported to be associated with an increased incidence, although rare, of hypertension and thromboembolic (arterial and venous) events. However, this association has been challenged recently by others.[14]

In 1987, Porter et al.[33] reported no association between OC use and stroke, myocardial infarction, or cardiovascular mortality. This was attributed to "newer formulations of OCs and greater care in prescribing."[33] In this study fatal cardiovascular events occurred only in nonusers of the pill. The Finnish study[14] mentioned previously supports this finding.

Now are the various risk indicators that clinicians measure in the blood truly of prognostic value, especially among OC users?

First, the extent of the increase in sex hormone–binding globulin induced by an OC pill formulation can be used as an indicator of its inherent estrogenicity.[34, 35] The HDL-C concentration in plasma is highest with hormones that have the greatest estrogen potency.[36] Estrogens, as well as estrogen-dominant OC formulations, increase not only sex hormone–binding

globulin and HDL-C (the latter, assumed to be beneficial for the development of atherosclerotic changes) but also total and very low–density lipoproteins triglycerides (which are considered detrimental to atherosclerotic changes) according to their estrogen potency.[36]

However, the inherent estrogenicity of an OC formulation depends on not only its estrogen content but also the type and amount of its progestogen.[34] Some progestogens have some inherent estrogenicity, such as ethynodiol diacetate and norethisterone. On the other hand, others have strong inherent antiestrogenic effects, such as levonorgestrel. Such an antiestrogenic effect is able to reverse or minimize desired and undesired estrogenic effects.[37]

In a prospective, longitudinal-controlled study that compares the metabolic and hemostatic effects of three low-dose OCs containing either levonorgestrel or desogestrel as progestogen (about 30 women in each group over a 12-month period) in Singapore, the low-dose, fixed levonorgestrel combination OC was the most neutral.[38, 39] The low-dose, fixed desogestrel pill was the most estrogenic formulation, inducing the greatest increase, as expected, not only of HDL-C but also of the triglycerides and coagulation factor VII. In addition, the desogestrel combination had the greatest adverse effect on the oral glucose tolerance test.[38, 39]

Thus what really is the mechanism of OC-associated cardiovascular events in OC users? Most other case-control studies, including a large prospective study in 119,061 nurses, found no evidence of an increased cardiovascular risk in past users of OCs.[40] The authors of this large prospective study concluded that their data do not support the hypothesis of OC-associated atherosclerosis but rather that OC-associated cardiovascular events are caused by the alteration in more acute processes, such as platelet function and coagulation.[40]

If the significant increase in mortality caused by myocardial infarction in the Royal College of General Practitioners' Study was the result of coronary atherosclerosis, then there should have been a time lag between the start of pill use and the increase in mortality. Considering the gradual development of atherosclerosis over many years, there should have been a significant association between duration of pill use and mortality rate. Neither is evident in the Royal College of General Practitioners' Study.[2]

Both the lack of a significant association between cardiovascular events with OC use and the absence of a time lag after the start of OC pill use strongly negate the hypothesis of any OC-associated atherosclerotic risk.

The following conclusions can be made: (1) The present epidemiologic evidence shows that the risk of OC use is generally confined to current users; there is no significant association between risk and duration of use and no time lag between risk and start of OC use. (2) Progestogens with a pronounced antiestrogenic (or better anti–ethinyl estradiol) effect are most suitable to reverse or minimize the strong effects of estrogens. (3) Likewise, a too-profound beneficial lipid profile induced by OC pills may be associated with a clinically more relevant adverse clotting profile. (4) A well-balanced, low-dose OC pill should alter any of the cardiovascular risk indicators as little as possible in either a supposedly positive or negative direction.

Only prospective long-term follow-up in large cohorts of women will be able to establish the relative safety of specific OC pill formulations. However, it has been shown in the so far largest cohort study, the Royal College of General Practitioners' Study, that the relative risk of acute myocardial infarction associated with ever use of combined OCs was 0.55 (95% confidence interval, 0.24 to 1.26) for levonorgestrel-containing pills, 1.0 for controls, and 1.24 for OCs containing other than levonorgestrel progestogens (95% confidence interval, 0.81 to 1.91).[41] A review of available literature shows that distinction cannot be made among various OCs concerning a possible increase or decrease in risk of atherosclerosis, and no data show that lowering or raising HDL-C with OCs promotes or retards atherosclerosis or premature atherosclerotic coronary heart disease.[42]

Gynecologists are very often the primary health care physicians for young women. In this role they join other primary health care physicians and the cardiology community in detecting and attacking cardiovascular risk factors, such as high serum cholesterol. This challenge dwarfs the largely hypothetical issue, of which low-dose OCs have the smallest effect on lipid parameters.[43]

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Clinical aspects of the relationship between oral contraceptives and abnormalities of the hemostatic system: Relation to the development of cardiovascular disease

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Epidemiologic evidence has established that oral contraceptives increase the risk of both arterial and venous thromboembolic disease. This is dose related in the case of the estrogen component for both arterial and venous events and in the case of progestogens for arterial events. It is probable that the increased rate of thromboembolic events caused by estrogen is related to hypercoagulability. Plasma levels of several clotting factors have been shown to be elevated in oral contraceptive users, and this increase is graduated according to the dose of estrogen. In pregnancy, factor VIIc is increased after cold activation of plasma at 4° C overnight. Likewise, in users of oral contraceptives, both factors VIIc and XIIc are increased, which suggests a direct effect of factor XIIc on the extrinsic system. In men, the risk of ischemic heart disease is strongly and independently related to factor VIIc and fibrinogen levels; thus it is possible that in women taking oral contraceptives, the mechanism of risk is similarly mediated. There is a good case for factor VIIc as the index of flux in the coagulation system and hence of a hypercoagulable state, and indeed it may directly contribute to the generation of thrombin. This article examines the available evidence on clotting factor activity in the risk of cardiovascular disease in oral contraceptive users. (AM J OBSTET GYNECOL 1990;163:392-5.)

Key words: Hypercoagulability, coagulation, factor VII, thrombin, fibrinogen, oral contraceptives

In this article I briefly review the general evidence of the risk of thrombosis in relation to oral contraceptive use and examine the separate contributions of the estrogen and progestogen components. I also discuss the contributions of the coagulation system to thrombogenesis and cite both epidemiologic and experimental data. I then look at what I believe is mainly an estrogen-mediated effect on clotting factors both in physiologic and pharmacologic circumstances. Finally, I summarize the general epidemiology of factor VIIc and fibrinogen, in particular emphasizing the circumstances under which increased risk may result for oral contraceptive users.

Oral contraceptives and risk of thromboembolism

There is good epidemiologic evidence of a relationship between thrombotic events, both venous and arterial, and use of oral contraceptives.[1] In the 20 years since Vessey and Doll[2] published their first case-control data, numerous studies have reported an association.[3-5] It should be noted that the dose of estrogen used has declined progressively over that 20-year period, as has the age and risk profile of oral contraceptive users, which means that more up-to-date epidemiologic data are necessary.

However, I will briefly summarize the results of some of these earlier studies, each of which has demonstrated a dose response for the two most commonly used estrogens, mestranol and ethinyl estradiol.[3-5] Although attention has principally focused on the estrogen component, type and strength of progestogen have varied considerably within each estrogen subgroup, so that in fact evidence of an estrogen effect, independent of progestogen, is relatively scant.[1]

In several studies, however, it has been possible to stratify the data by the strength of the estrogen dose and thereby examine the independent influence of progestogen.

The data of the Committee on Safety of Drugs analyzed by Inman et al.[3] in 1970, clearly showed a significant trend for venous thromboembolism, cerebral

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Table I. Mean ± standard error of factor VIIc, fibrinogen, and systolic blood pressure levels by estrogen dose in Northwick Park Heart Study participants

	Not using OCs (n = 243)	*30 μg (n = 15)*	*50 μg (n = 63)*
Factor VII (%)	83.0 ± 1.4	96.6 ± 8.6	121.1 ± 4.4
Fibrinogen (gm/L)	2.52 ± 0.4	2.84 ± 0.1	2.89 ± 0.9
Blood pressure (mm Hg)	117.5 ± 1.0	129.7 ± 4.0	125.3 ± 2.0

OCs, Oral contraceptives.

thrombosis, and coronary thrombosis, by the dose of estrogen, although some variability in the pattern led these authors to propose a separate progestogen effect. The rates of venous thrombosis by estrogen dose in the Royal College of General Practitioner Study[4] were also clearly significant and dose dependent. The data of the Committee on Safety of Medicines[5] demonstrated significant increases in total mortality and ischemic heart disease. However, one puzzling observation at the time was the inverse pattern for weight gain and headache, which again suggested progestogen effect, since levonorgestrel was the progestogen in 30 μg estrogen preparations, whereas a different progestogen, norethisterone acetate, was in many 50 μg estrogen preparations.

The Royal College of General Practitioners Study demonstrated increased rates of both hypertension and arterial disease, with different doses of progestogen given constant doses of estrogen, although the data on 30 μg ethinyl estradiol in combination with 150 μg levonorgestrel is relatively sparse.[4] Likewise, the data of the Committee on Safety of Medicines showed a graduated pattern of risk of arterial events for both norethisterone acetate and levonorgestrel.[5]

Therefore there is a definite dose-response relationship with both estrogen and progestogen, although the mechanisms of risk may be quite different, with the estrogen effect being mostly on coagulation, whereas the progestogen effect is on lipid metabolism and blood pressure.[1]

The coagulation system and thrombosis

The specific contribution of this system to the risk of thrombosis has received renewed attention in recent years. In this regard an important contributor has been the prospective Northwick Park Heart Study.[6]

This study examined the number of ischemic heart disease events after 5 years of follow-up, which was divided into tertiles by level of factor VII coagulant activity, fibrinogen, and cholesterol. A clear, graduated, and highly significant trend is apparent for risk of ischemic heart disease. This study was the first and largest to confirm the relative contribution of the clotting factors, although several other prospective studies have since done so,[7-10] thus confirming their importance as predictors of risk. Although one cannot necessarily extrapolate to women, there is no significant sex difference in factors (other than oral contraceptives) influencing the coagulation variables.

Oral contraceptives and the coagulation system

It has been known since 1966 that oral contraceptives can influence the levels of clotting factors.[11] Postmenopausal hormone replacement studies with estrogen only have demonstrated the same effect on clotting factors,[12] implying that it is the estrogen rather than the progestogenic component that is responsible.

In the Northwick Park Heart Study data,[13] which also included women (although not in sufficient numbers to assess outcome of ischemic events), a clear, graduated pattern between nonusers, those receiving 30 μg, and those receiving 50 μg of estrogen is apparent for both factor VIIc and fibrinogen (Table I). Blood pressure levels were higher in users compared with nonusers, which is again thought to be related to the progestogen constituent, because levels in the group receiving 30 μg of estrogen were actually higher than those receiving 50 μg, of which the chief difference between the two groups was the type of progestogen used. It is probable that the effect of the progestogen on cardiovascular events is mediated mainly through hypertension as a risk factor and the effects on lipid metabolism.

Factor VII forms a complex with tissue factor constituting the extrinsic system, which leads to activation of factor X and ultimately culminates in the formation of thrombin. The atheromatous plaque provides the tissue factor stimulus for the triggering of factor VII. In addition, it has become increasingly clear that factor VII may be directly activated by the Hageman factor (XII) and that factor XII itself may in turn be activated by factors as yet unknown within the circulation; the chief contenders are negatively charged fatty acid particles on circulating lipoproteins.[14, 15] Factor VII functions as an index of coagulability of the clotting cascade but may also directly contribute to the production of thrombin. Miller et al.[16] demonstrated that in cold activated plasma, there was a correlation between the increase in factor VIIc levels and that in fibrinopeptide A concentration, which in turn is an index of thrombin activity. Furthermore, factor VII activity was uninhibited by the addition of hirudin, which normally suppresses thrombin, thus suggesting that factor VII activity does indeed directly affect its

Table II. Summary of conditions in which factor VIIc and fibrinogen show variability

Higher levels	
Factor VIIc	Fibrinogen
Age	Age
Obesity	Obesity
Diabetes	Diabetes
Fat-rich diet	Smoking
OC use	OC use
Menopause	Menopause
	Lower socioeconomic group
Lower levels	
Black ethnic group	
Vegetarianism	

OC, Oral contraceptive.

production rather than vice versa. The current Thrombosis Prevention Trial[17] involves the administration of warfarin to men at high risk of developing ischemic heart disease with a dose sufficient to prolong the INR (international normalized ratio) to about 1.6 and hence reduce factor VII activity to about 70% of standard. This trial should help to clarify the effect of factor VIIc modification in relation to risk of thrombosis.

Therefore clotting factors are important as predictors of thrombosis, and I have summarized some of the evidence for their causative contribution.

Estrogen, coagulation variables, and thrombosis

I will now review some additional reasons for believing that estrogen fluctuation influences clotting ability.

Gordon et al.[18] have also examined factor VIIc in users of oral contraceptives. They have shown a clear correlation between factor VII and XII activity in both users and nonusers of oral contraceptives after cold activation, with appreciably higher levels in the former group. This phenomenon of increased activity after exposure to cold in vitro is not just seen in the artificial situation of exogenous, administered estrogens, but can also arise in physiologic situations. The plasma of healthy pregnant women[15] was compared with that of a group of control nonpregnant women, and here too factor VII activity was increased both when measured fresh and after cold activation. There are, of course, many hormone-induced changes during pregnancy with widespread effects on the lipid profile[15] so that the picture is certainly complex. However, these data confirm that in an environment of considerable endogenous hormonal variation, clotting activity is likely to be appreciably increased.

There has been interest for many years in estrogen levels as a risk factor for myocardial infarction in both men and women and in a variety of situations and thus the topic is not new.[19] However, a recent study on treatment with exogenous estrogens for carcinoma of the prostate gland showed an appreciably increased risk in the incidence of cardiovascular events in such patients compared with those randomized to orchidectomy only. An analysis of factor VIIc 6 weeks after randomization revealed a 50% increase in the estrogen group with a fall in the relatively protective antithrombin III.[20, 21]

Factor VIIc, fibrinogen, and factors influencing variability

Table II summarizes the salient epidemiologic associations of factor VIIc and fibrinogen. This is of some interest because it not only shows a tendency for increased levels of both factors in pill users per se, but also in a variety of other situations known to aggravate risk in users of oral contraceptives. There is considerable sensitivity to dietary variation of factor VII coagulant activity and a tendency for increased levels in overweight persons.[22]

The results of the Northwick Park Heart Study on the relationship between cigarette smoking and fibrinogen show higher levels in smokers generally, which decrease to levels comparable with nonsmokers after about 5 years,[23] thereby confirming the importance of this habit in influencing variation in fibrinogen levels. There is also a dose-response relationship.[24] The significance of smoking status as a predictor of risk of myocardial infarction in current users of oral contraceptives has recently been reemphasized in the Royal College of General Practitioners Study, in which current users of oral contraceptives who smoked more than 15 cigarettes per day had a 20-fold increase in relative risk of myocardial infarction.[25]

In summary, factor VIIc and fibrinogen levels are strongly predictive of ischemic events in men, so it seems possible that this is also the case in women. Oral contraceptives influence the risk of thromboembolic events in a dose-dependent way, and at least some of this risk may be mediated through the effects of estrogen on the coagulation system, in particular on factor VIIc and fibrinogen. In addition, the general profile of cardiovascular risk in users of oral contraceptives relates to the known effects on fibrinogen and factor VIIc. It is likely that abnormalities in the coagulation system are important contributors to the risk of thrombosis in oral contraceptive users.

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Effects of newer oral contraceptives on the inhibition of coagulation and fibrinolysis in relation to dosage and type of steroid

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Oral contraceptives influence plasma proteins, causing changes in plasma procoagulants and fibrinolytic effectors. Estrogen is thought to be responsible for these changes, whereas progestogens, in particular those with an androgenic effect, may influence the magnitude of the changes. This concept is consistent with epidemiologic studies, suggesting a correlation between estrogen dose and cardiovascular episodes in oral contraceptive users. A delayed resolution of fibrin might contribute to an increased risk caused by decreased coagulation inhibition or fibrinolytic efficacy. Estrogen (30 μg or more) has a dose-dependent effect on clotting factors, including antithrombin III and proteins C and S. The effect of high- and low-dose oral contraceptives containing various progestogens on the fibrinolytic system is less clear. We have found that low-dose oral contraceptives containing levonorgestrel or lynestrenol enhance fibrinolysis, as revealed by an increase in plasminogen (30% to 40%), a decrease in histidine-rich glycoprotein (15% to 26%), an increase in tissue plasminogen activator activity (>150%), and a decrease in tissue plasminogen activator inhibition (30% to 40%), concomitant with a slight decrease in tissue plasminogen activator antigen level (15% to 20%). New oral contraceptives contain less androgenic progestogens. Preliminary results of an ongoing study of women receiving either 20 μg of ethinyl estradiol with 150 μg of desogestrel or 30 μg of ethinyl estradiol plus 75 μg of gestodene revealed no change or changes similar to the older low-dose preparations after 6 months of treatment. Of particular importance was the finding that coagulation activation, expressed by the levels of thrombin–antithrombin III-complexes, fibrin formation, and the efficacy of fibrinolysis, expressed by the levels of fibrin degradation products, was identical in the two groups. (Am J Obstet Gynecol 1990;163:396-403.)

Key words: Oral contraceptives, coagulation, fibrinolysis, gestodene, desogestrel, ethinyl estradiol

Since the first report of a possible association between the use of combined oral contraceptives (OCs) and thrombotic disease,[1] the risk of cardiovascular complications, such as venous and arterial thrombosis and embolism, myocardial infarction, and cerebral thrombosis, has been under debate,[2] and it must be concluded that the discussion has not yet reached a stage of final agreement. Several retrospective (case-control) and prospective (cohort) studies have suggested an increased risk of cardiovascular disease.[2-4] However, the studies have been exposed to criticism, such as a lack of objective diagnosis and the involvement of additional risk factors, particularly smoking and age, which may account for a substantial portion of the observed cardiovascular complications.[5, 6]

Several studies have provided evidence that the risk of cardiovascular events is related to the content of estrogen and also the progestogen concentration.[4, 7, 8] Thus until recently the strategy to reduce the side effects of OCs has primarily been to reduce the steroid dose, and in the past few years, OCs containing 30 μg of estrogen have been available. Very recently OCs containing 20 μg of estrogen have been introduced into the market, and new, more selective progestogens with a high affinity to the pituitary-ovarian axis and reduced metabolic effects have been developed.

Several attempts have been made to support the epidemiologic explanations on the basis of observed deviations within the fields of lipid and glucose metabolisms or the hemostatic system. Although there is an important limitation of the extent to which information from these studies can contribute to the debate on vascular disease and OCs, these studies have provided valuable information with respect to the various metabolic effects of OCs, and have, to a certain extent, provided a link between the consumption of OCs and the reported incidence of vascular disease.[9] Such a conclusion would be in agreement with the recent Consensus Report on OCs,[10] which recommends the use of OCs with the smallest metabolic effects compared with normals.

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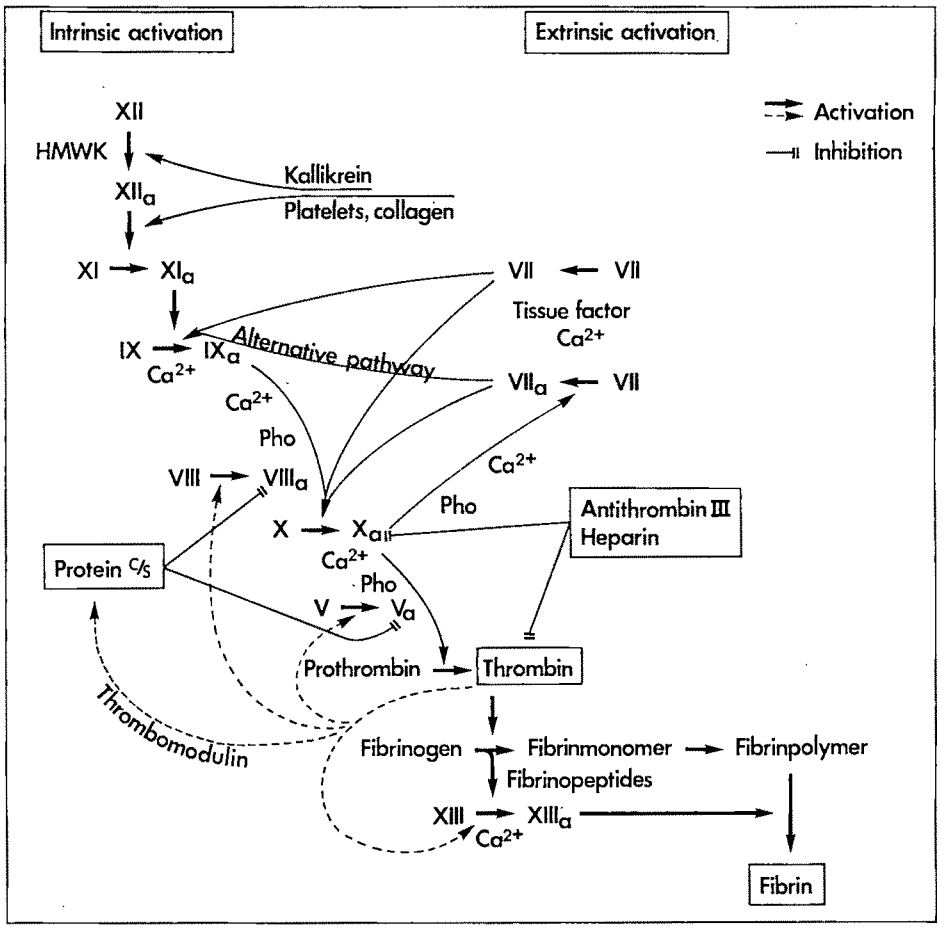


Fig. 1. A simplified scheme of the coagulation system. Factor and synonym name: *Factor I,* Fibrinogen; *factor II,* prothrombin; *factor III,* tissue thromboplastin; *factor IV,* calcium ions; *factor V,* proaccelerin; *factor VII,* proconvertin; *factor VIII,* antihemophilic factor A; *factor IX,* antihemophilic factor B (Christmas factor); *factor X,* Stuart-Power factor; *factor XI,* plasma-thromboplastin antecedent; *factor XII,* Hageman factor; *factor XIII,* fibrin-stabilizing factor; *HMWK,* High molecular–weight kinogen (Fitzgerald factor); *prekallikrein/kallikrein,* Fletcher factor; *Pho, phospholipid.*

This review summarizes the present knowledge of the dynamic hemostatic balance and the possible consequences of deviations from this balance with particular reference to so-called low-dose estrogen OCs. Thus the scope of this review covers coagulation, and in particular the fibrinolytic system, taking into account the recent understanding of thrombosis mechanisms. Finally, we describe an ongoing study that uses third-generation progestogens at different dosages established to examine the effects of the coagulation and fibrinolysis system on various selected variables and discuss some of the preliminary results.

The concept of dynamic hemostatic balance

The mechanisms of hemostasis protect the integrity of the vascular system so that in case of injury, the tissues are healed, and their function is restored and secured. Hemostasis and tissue repair are complex processes in which many cellular and humoral components participate. The hemostatic process depends on interactions between the vascular endothelium, the platelets, and the processes of blood coagulation and fibrinolysis. Nevertheless, Astrup[11, 12] developed and introduced the concept of a dynamic hemostatic balance, which has been valuable in clinical work. The balance might be characterized by its capacity or *degree* of *activation*, taking into account the introduction of new molecular markers that reflect activation of the coagulation and fibrinolytic systems[9, 13] (see the article by Dr. Kluft in this supplement). In the more acute disease states, the concept might be described as a thrombohemorrhagic balance.[9]

Regulation of the formation and resolution of fibrin

Several mechanisms, both local and humoral, participate in the regulation of fibrin formation and resolution.[9, 13, 14] Two systems regulate the formation, position, and resolution of fibrin in the organism. The coagulation system (Fig. 1) generates an enzyme throm-

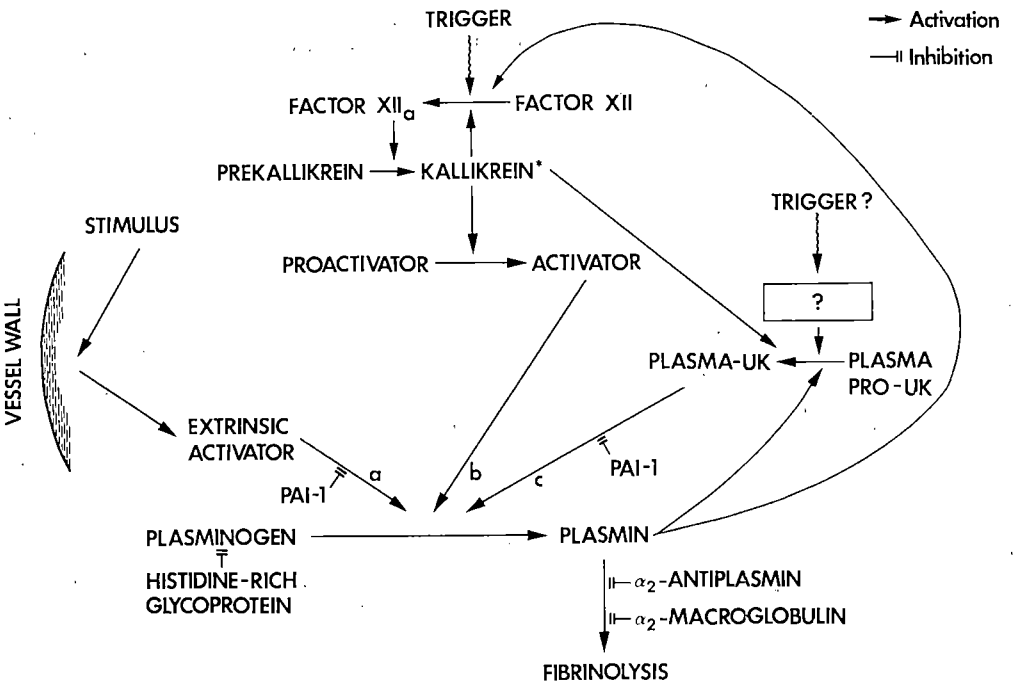


Fig. 2. Initiation of fibrinolytic activity in plasma by extrinsic *(a)* and intrinsic pathways *(b-c)*. (See text for details.) *UK*, Urokinase.

Table I. Coagulation inhibition potential: A comparison between treatment

Variables	*20 μg ethinyl estradiol; 150 μg desogestrel (n = 10)*	*30 μg ethinyl estradiol, 75 μg gestodene (n = 9)*
Antithrombin III: Ag (%)	97 ± 3	99 ± 5
Protein C: Ag (%)	103 ± 14	102 ± 10
Total protein S: Ag (%)	93 ± 12	86 ± 7

Mean ± 2 SEM.
Ag, Antigen.

bin, which is able to convert fibrinogen into a fibrin gel. The system of fibrinolysis (Fig. 2) produces the fibrin-dissolving enzyme plasmin. Several activating stages participate in the conversion of the enzyme procursors, prothrombin and plasminogen, to the active enzymes. Inhibitors of various types regulate or block the generation of the active compounds and their action (Figs. 1 and 2). At a site of injury of the vessel wall, thromboplastic compounds are released from damaged cells and clot-promoting endothelial and subendothelial structures are exposed, which may activate the extrinsic and intrinsic coagulation pathways of thrombin formation. Similarly, plasmin can be produced through two different pathways (Fig. 2). One of these, the extrinsic pathways, is initiated by activators released from the endothelial cells into circulation, that is, tissue-type plasminogen activator (t-PA). The intrinsic pathway depends on the formation of activators from humoral precursors belonging to the factor XII–dependent or factor XII–independent system (now termed the "prourokinase system").[9, 13, 15]

OCs and the coagulation system

Numerous investigators have reported on changes in the levels of various plasma components belonging to the coagulation system, and the effects of OCs have been summarized in numerous articles.[9, 16, 17] The changes have been reported most consistently in the four vitamin K–dependent factors— II, VII, XI, and X. As described elsewhere,[16, 18] it is questionable whether such changes predispose to a hypercoagulable state. However, the importance of decreased inhibition of blood coagulation in the pathogenesis of thrombotic disease has been underscored by clinical observations, particularly in relation to antithrombin III heparin and the protein C/protein S systems. We may describe the condition in patients with a deficiency in one of these components leading to thrombosis as thrombophilia.

Determination of antithrombin III concentration, the main physiologic inhibitor of thrombin, by an immunologic method or a more specific, functional method by means of a synthetic peptide substrate for thrombin and in the presence of heparin, has showed little or no difference in the levels between normal women and women receiving OCs containing 30 or 50 μg of ethinyl estradiol, but a slight fall, <10%, within groups of women taking these OCs.[19-21]

Few studies exist on the effect of OCs on the other

Table II. Coagulation inhibition potential: A comparison between circumstances (0 to 6 months)

	20 μg ethinyl estradiol, 150 μg desogestrel			*30 μg ethinyl estradiol, 75 μg gestodene*		
Variable	*No.*	*Before*	*During*	*No.*	*Before*	*During*
Antithrombin III: Ag (%)	10	97 ± 4	98 ± 5	9	101 ± 5	100 ± 4
Protein C: Ag (%)	10	96 ± 11	103 ± 14	9	89 ± 11	106 ± 14
Total protein S: Ag (%)	10	102 ± 14	88 ± 12*	9	102 ± 9	83 ± 10*

Mean ± 2 SEM.
Ag, Antigen.
*Different from initial values with $p < 0.01$.

Table III. Coagulation activation: A comparison between treatment

Variable	*20 μg ethinyl estradiol, 150 μg desogestrel (n = 10)*	*30 μg ethinyl estradiol, 75 μg gestodene (n = 9)*
TAT complexes: Ag (μg/L)	3.4 ± 0.9	3.8 ± 0.9

Mean ± 2 SEM.
TAT, Thrombin–antithrombin III; *Ag,* antigen.

Table IV. Coagulation activation: A comparison between circumstances (0-6 months)

	20 μg ethinyl estradiol, 150 μg desogestrel			*30 μg ethinyl estradiol, 75 μg gestodene*		
Variable	*No.*	*Before*	*During*	*No.*	*Before*	*During*
TAT complexes: Ag (μg/L)	10	2.9 ± 0.8	2.9 ± 0.5	9	3.8 ± 1.0	3.2 ± 1.4

Mean ± 2 SEM.
TAT, Thrombin–antithrombin III; *Ag,* antigen.

main components inhibiting coagulation—protein C and protein S. Both are vitamin K–dependent–specific plasma proteins. Protein C inactivates blood clotting factors V_a and VIII_a, and protein S serves as a cofactor for activated protein C.[22, 23] Recent reports have revealed no significant changes in the concentration of protein C in women taking OCs containing 30 μg of ethinyl estradiol[24] or unchanged or slightly increased concentrations in women taking OCs with 30 μg of ethinyl estradiol.[25-28] Conflicting results have been reported on protein S determined by different methods.[25-31] Furthermore, these studies have not considered either the type of consumption of the OC preparation or the period of blood sampling during the hormone-induced cycle. Using an assay procedure that measures total protein S, we recently reported no difference between normal women and those taking OC containing 30 μg of ethinyl estradiol, although there was a slight decrease during hormone consumption.[32]

Apparently the changes in various coagulation factors are related to the dose-dependent effect of estrogen, but the estrogen/progestogen ratio and the type of progestogen also seemed to be important.

From our ongoing study in young healthy women of the effect of two new monophasic, low-dose preparations containing new third-generation progestogens, desogestrel or gestodene, the preliminary results of the determination of the clinically relevant inhibition potential are shown in Tables I and II. There was no difference between types of treatment, that is, the treatment period is ignored by analysis on the average of each woman of the values for each sampling period or after 6 months of treatment (circumstances, Table II); antithrombin III and protein C were not significantly changed statistically, whereas total protein S decreased within the two groups, but the ranges of total protein S did not differ.

The degree of activation of the coagulation system was also assessed with plasma concentrations of thrombin–antithrombin III complexes used as a marker of thrombin formation. The concentration in plasma of thrombin–antithrombin III complexes was determined by an enzyme-linked immunosorbent assay method.[33] Regarding both treatment and the period of treatment (Tables III and IV), no significant changes were observed, and the two groups did not differ.

Table V. Fibrinolytic potential: A comparison between treatment

Variable	*20 μg ethinyl estradiol, 150 μg desogestrel (n = 10)*	*30 μg ethinyl estradiol, 75 μg gestodene (n = 9)*
Plasminogen: Ag (%)	121 ± 10	130 ± 7
Histidine-rich glycoprotein: Ag (%)	107 ± 24	105 ± 20
t-PA: Ag (ng/ml)	7.2 ± 5.9	5.1 ± 0.9
PAI-1: Ag (ng/ml)	6.0 ± 3.2	6.3 ± 3.2
t-PA activity (IU/ml)	0.17 ± 0.09	0.19 ± 0.11

Mean ± 2 SEM.

Table VI. Fibrinolytic potential: A comparison between circumstances (0-6 months)

	20 μg ethinyl estradiol, 150 μg desogestrel			*30 μg ethinyl estradiol, 75 μg gestodene*		
Variable	*No.*	*Before*	*During*	*No.*	*Before*	*During*
Plasminogen: Ag (%)	10	99 ± 7	134 ± 12*	9	103 ± 4	143 ± 12*
Histidine-rich glycoprotein: Ag (%)	10	124 ± 32	101 ± 22†	9	131 ± 27	95 ± 19†
t-PA: Ag (ng/ml)	10	5.1 ± 1.4	4.5 ± 1.4	9	6.2 ± 0.9	5.1 ± 1.8
PAI: Ag (ng/ml)	10	9.2 ± 4.5	6.2 ± 4.8	9	9.3 ± 3.8	8.1 ± 7.0
t-PA activity (IU/ml)	10	0.08 ± 0.04	0.16 ± 0.08‡	9	0.06 ± 0.03	0.26 ± 0.18‡

Mean ± 2 SEM.

*,†Different from initial values with $p < 0.01$.

‡Different from initial values with $p < 0.05$.

OCs and the fibrinolytic system

Despite an increasing knowledge of the fibrinolytic system with its various extrinsic and intrinsic pathways of activation (Fig. 2),[9, 13, 15, 34, 35] until now the clinical relevance of any deviation has mainly been associated with the extrinsic or the tissue plasminogen activator (t-PA) system, that is, the relationship between t-PA and its fast-acting plasminogen activator inhibitor type 1 (PAI-1).[13, 36]

The t-PA is produced by the endothelial cells and is secreted into the blood by mechanisms still unknown. Various stimuli and agents such as stress, exercise, catecholamines, nicotinic acid, and vasopressin analogs increased the release of t-PA from the tissue stores.[15, 35] Secretion of t-PA into the blood does not immediately result in activation of the fibrinolytic system, because in the absence of fibrin, t-PA has a very low affinity for plasminogen. However, when an intravascular clot is formed, t-PA and plasminogen bind sequentially to fibrin, resulting in the rapid generation of plasmin. This means that physiologic fibrinolysis requires fibrin not only as a substrate, as implied by the terminology, but also that fibrin acts as a stimulatory cofactor in plasminogen activation.[36, 37] PAI-1 is produced by hepatocytes, endothelial cells, and presumably megakaryocytes.[38] In the systemic circulation t-PA and PAI-1 are the major determinants of the so-called spontaneous fibrinolytic activity of blood. The introduction of new assays in recent years has made the determinations of fibrinolytic activity and the involved components not only more specific but also more reliable.

The hitherto available reports on the effects of high- and low-dose OCs on the t-PA/PAI-1 system and containing various progestogens are not that clear.

Recent studies in low-dose OCs have shown that after 3 months of treatment, t-PA activity and inhibition increased and decreased, respectively,[39, 40] as during one hormone-induced cycle[41, 42] and that the t-PA antigen level also decreased. Thus both long- and short-term administration of OCs containing 30 μg of ethinyl estradiol and 150 μg of levonorgestrel or 37 μg of ethinyl estradiol and 750 μg of lynestrenol revealed the same t-PA/PAI-1 pattern. This statement has recently been confirmed by Siegbahn and Ruusuvaara,[43] who also showed a highly age-dependent increase in t-PA antigen concentrations in normal women.

The preliminary data from our ongoing study are shown in Tables V and VI. The plasma samples were obtained from fasting persons in the morning.[44] The t-PA activity was determined in plasma euglobulin fractions by the parabolic rate assay described by Verheijen et al.[45] and expressed in international units per milliliter. The total antigen concentration in plasma of t-PA and PAI, both expressed as nanograms per milliliter, were assessed by enzyme-linked immunosorbent assay methods (Biopool Imulyse 5-t-PA and Biopool Tint-

Table VII. Fibrinolytic efficacy: A comparison between treatment

Variable	*20 μg ethinyl estradiol, 150 μg desogestrel (n = 10)*	*30 μg ethinyl estradiol, 75 μg gestodene (n = 9)*
FbDP (μg/L)	0.20 ± 0.04	0.19 ± 0.03

Mean ± 2 SEM.
FbDP, Fibrin degradation product.

Table VIII. Fibrinolytic efficacy: A comparison between circumstances (0 to 6 months)

	20 μg ethinyl estradiol, 150 μg desogestrel			*30 μg ethinyl estradiol, 75 μg gestodene*		
Variable	*No.*	*Before*	*During*	*No.*	*Before*	*During*
FbDP (μg/L)	10	0.18 ± 0.12	0.20 ± 0.06	9	0.15 ± 0.03	0.22 ± 0.05*

Mean ± 2 SEM.
FbDP, Fibrin degradation product.
*Different from initial value with $p < 0.05$.

Elize PAI-1, Biopool, Umeå, Sweden). The antibody used in the assay of PAI-1 detects equally well free PAI-1 and PAI-1 bound to activators. There were no differences between the two study groups with respect to the concentrations of t-PA and PAI-1 antigens and t-PA activity, which represent the systemic balance between t-PA and PAI-1 (Table V). However, in both groups during 6 months of treatment (Table VI), there might, despite the lack of statistical significance, be a relevant decrease in t-PA antigen level, and in particular in PAI-1 level, because t-PA activity increased significantly within both groups.

Binding of plasminogen to fibrin depends on the so-called lysine-binding sites of the plasminogen molecule. Histidine-rich glycoprotein is a plasma protein that binds to these sites, thereby decreasing the concentration of free genuine plasminogen, possibly providing a regulatory mechanism of fibrinolysis.[46]

A significant increase in plasminogen and a decrease in histidine-rich glycoprotein in plasma have been reported in studies with OCs containing <50 μg of ethinyl estradiol and containing various progestogens.[39, 47, 48] Whether this actually results in an increase in fibrinolytic capacity in women receiving OCs remains to be determined. The observed decrease in plasma histidine-rich glycoprotein was recently confirmed and found to be caused by the estrogen component.[49]

Preliminary data from our ongoing study are shown in Tables V and VI. Neither histidine-rich glycoprotein nor plasminogen differs with respect to the type of treatment, whereas within both groups, there were a significant increase in plasminogen and a decrease in histidine-rich glycoprotein, respectively, and within the same order of magnitude as previously reported.[39, 47, 48]

The fibrinolytic efficacy was estimated by a specific measurement of fibrin degradation products, and the results were expressed as micrograms per milliliter according to a calibrator delivered from the manufacturer.[50] We found no difference between treatment (Table VII), but during the treatment period, there was a slight increase within the group receiving 30 μg of ethinyl estradiol (Table VIII). No data are available in the literature for any comparison.

Concluding remarks and perspectives

The overall impression of our preliminary evaluation of two OC preparations containing third-generation progestogens is that the changes in several relevant variables within the dynamic hemostatic balance are in the same ranges, which suggests that they are independent of the ratio of estrogen/progestogen components. Moreover, the observed small changes, if any, are of the same order of magnitude as in our previously published studies[41, 42, 47, 48] and in the comprehensive study by Gevers Leuven et al.[39] This suggest an absence of a selective effect of the newer preparations, at least with respect to the hemostatic system. The lack of ratio-dependent changes might suggest a low synergistic or antagonistic effect of the progestogens.

Furthermore, the described observations seem to point to the absence of an effect on the hemostatic balance significant enough to be a possible cause of an increased risk of cardiovascular disease in normal women, as discussed extensively elsewhere.[9] In this respect the dynamic assessment of interaction between blood and the vessel wall as described by Baumgartner[51] is of particular interest and perhaps may be a relevant test to be included in future evaluations. In this model subendothelium of rabbit aorta is exposed to flowing nonanticoagulated blood in an annular flow chamber at a shear rate corresponding to the human venous system and middle-size arteries. Increased deposition

of fibrin and platelet thrombi was observed in women using OCs containing 50 μg of ethinyl estradiol[51] compared with healthy control subjects, whereas no difference was observed in women using OCs containing 20 μg of ethinyl estradiol.[52]

To verify or reject a possible link between the biochemical and epidemiologic findings, further experimental studies on the mechanisms of the effects of OCs on the hemostatic balance prospective clinical studies are needed. Furthermore, it is also extremely important to try to establish an integrated concept with respect to the hemostatic system and the carbohydrate and lipid systems. Without such an interrelated interpretation of obtained data, any evaluation might be difficult.

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Studies on the mechanism of action of oral contraceptives with regard to fibrinolytic variables

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Evidence is provided that the fibrinolytic capacity in plasma is strongly dependent on circulating concentrations of tissue plasminogen activator rather than on concentrations of plasminogen activator inhibitor. Thus a decrease in plasma tissue plasminogen activator concentrations, as is the case in oral contraceptive users, may result in a decrease in plasma fibrinolytic capacity despite a parallel decrease in plasminogen activator inhibitor levels. It is now clear that the presence of specific intracellular receptors and a given motif in the genome are essential to mediate hormone-dependent regulation of gene expression. A computer search revealed potential estrogen and glucocorticoid-progesterone–responsive elements in the genes coding for tissue plasminogen activator, plasminogen activator inhibitor, and some other fibrinolytic variables. No convincing evidence for the presence of sex steroid receptors in endothelial cells was found, but liver cells clearly contain estrogen and androgen receptors. However, neither endothelial cells nor hepatocytes cultured in vitro showed a change in tissue plasminogen activator or plasminogen activator inhibitor synthesis on incubation with sex steroids (10^{-9} to 10^{-6} mol/L) for 3 days. An alternative explanation for the observed decreases in tissue plasminogen activator and plasminogen activator inhibitor concentrations in the plasma of oral contraceptive users is discussed. (Am J Obstet Gynecol 1990;163:404-12.)

Key words: Oral contraceptives, fibrinolysis, regulation, endothelial cells, hepatocytes

Some epidemiologic studies have suggested an association between an increase in the incidence of thromboembolic disease and the use of oral contraceptives,[1] especially for women over the age of 35 years and those who smoke.[2] The incidence of thromboembolic disease in oral contraceptive users has decreased strongly since the introduction of low-estrogen preparations, but some risk of vascular disease may still persist.[3]

Several investigators have studied the possible effects of oral contraceptive consumption on fibrinolysis, since the fibrinolytic system is generally believed to play a crucial role in the maintenance of blood vessel patency. The clinical importance of the fibrinolytic system is demonstrated by reports of a strong correlation between malfunctioning of the fibrinolytic system and hemostatic disorders.[4] Indeed, the use of oral contraceptives is associated with changes in the plasma levels of several proteins involved in the fibrinolytic system.[5-8] However, these studies of fibrinolysis in women using oral contraceptives point to an increase in blood fibrinolytic activity, which seems difficult to reconcile with an increased risk of cardiovascular disease.

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The aim of the present article is twofold. First, evidence will be presented that the increase in fibrinolytic capacity in plasma from oral contraceptive users, as observed in in vitro tests may not reflect the in vivo situation. Reassessment of existing data according to our current view indicates diminished rather than increased fibrinolytic activity in the plasma of women using oral contraceptives. Insight into the regulation of the synthesis of relevant fibrinolytic variables and the effect of various pill components thereupon might ultimately enable us to design in a rational way, oral contraceptive compositions that will minimally affect the plasma fibrinolytic system. For that purpose, we will later discuss what has been learned in the past few years about the molecular mechanism of steroid hormone action, with particular reference to the synthesis of fibrinolytic components. Furthermore, we have used cultured human endothelial cells and human hepatocytes as an in vitro model system to study the regulation of essential fibrinolytic variables and the effect of various steroid hormones thereupon. The validity of this model system will be discussed.

Initiation and regulation of fibrinolysis in human plasma

Fibrinolytic activity in plasma is largely initiated by plasma plasminogen activators which generate the fibrin-degrading enzyme plasmin from its precursor

plasminogen. Because of the exceptionally low[9, 10] and labile[11] nature of plasma fibrinolytic activity in vitro, few investigators have directly studied fibrinolysis in plasma. Instead, most efforts have been directed toward study of purified components and euglobulin. The latter approaches have, according to Wun and Capuano,[12] "the limitation that important regulatory components are completely or partially eliminated . . ." However, in the most complex and undisturbed system with nonanticoagulant fresh whole blood, no spontaneous lysis occurs unless plasminogen activators are added.[13] The most complex system that still shows spontaneous lysis is described by Wun and Capuano[12, 14] and concerns a plasma clot lysis assay in which lack of lysis is overcome by avoiding fibrin cross-linking. Using this system, they demonstrated that in vitro spontaneous plasma fibrinolysis is strictly dependent on tissue plasminogen activator (t-PA)–related protein but not on urokinase plasminogen activator (u-PA) or factor XII/kallikrein, suggesting that t-PA is possibly the primary initiator of fibrinolysis in the plasma milieu. The previously demonstrated contributions of urokinase plasminogen activator and factor XII/kallikrein in euglobulin assay systems[15] are apparently not expressed in the plasma system.

Also, studies on the importance of inhibitors of clot lysis have been carried out in the plasma milieu.[12] In unclotted plasma there is a loss of t-PA-induced fibrinolytic activity which is correlated with the formation of a complex between t-PA and a specific inhibitor, plasminogen activator inhibitor-1 (PAI-1). The addition of free t-PA to t-PA-depleted plasma followed by immediate clotting results in a high rate of fibrinolysis. In contrast, when free t-PA is allowed to incubate in plasma for periods up to 60 minutes before clot formation, the fibrinolytic activity of t-PA is gradually lost. These results suggest that free t-PA is susceptible to complexation with PAI-1 in the absence of a clot: fibrin formation renders t-PA relatively inaccessible to inhibition even though the surrounding serum contains more inhibitor than t-PA.

There may be little physiologic significance to the reaction between t-PA and the "slow" inhibitors, α_2-antiplasmin, α_2-macroglobulin, and C1-inhibitor. The concentration of each of these inhibitors is about 1 μmol/L, but the reactivity with t-PA is low: the second-order rate constant for the reaction between t-PA and α_2-antiplasmin (the fastest of these reactions) is about 10^2 mol/L · s^{-1} [16] compared with 10^7 mol/L · s^{-1} for the reaction between t-PA and PAI-1.[17, 18]

How do these mechanisms of clot lysis relate to the regulation of t-PA-dependent fibrinolysis in the circulation? We can assume that t-PA is released into the circulation as free t-PA. The reaction between t-PA and PAI-1 is very fast, but because both components are highly diluted and circulate normally at levels of 0.01 to 0.3 and 0.06 to 3 nmol/L, respectively, the reaction takes 10 minutes to 1 hour to reach a high degree of completion.[4, 12] On the other hand, both t-PA and PAI-1 are rapidly cleared from the circulation; for example, for t-PA a circulatory half-life of about 4 to 10 minutes in humans has been reported[19-21] and for PAI-1, a half-life of about 10 minutes.[21] The continuous release and the relatively short retention times of t-PA and PAI-1 in the circulation compared with the time needed to complete the reaction between t-PA and PAI-1 does allow that in the circulation free t-PA and PAI-1 activity can coexist.

Thus in summary, the following model for the initiation and regulation of t-PA dependent fibrinolysis in the circulation can be imagined. In the absence of fibrin, released tissue plasminogen activator molecules are partially complexed to PAI-1 before clearance from the circulation. In the event of fibrin formation, free t-PA is adsorbed onto fibrin, which renders t-PA relatively inaccessible to inhibition by PAI-1 and other putative t-PA inhibitors in the plasma. The fibrin-bound t-PA activates the fibrin-bound plasminogen to plasmin, which degrades the fibrin. It is, among others, by this mechanism that fibrinolysis is highly fibrin localized and efficiently regulated at the plasminogen activator level.

Supportive evidence for this model has come from recent studies by Colucci et al.[22] These investigators studied the influence of endotoxin-induced elevated plasma levels of PAI-1 on thrombolysis in rabbits with a jugular vein thrombus. Infusion of t-PA resulted in a dose-dependent degree of thrombolysis that was similar in both control and endotoxin-treated rabbits, although virtually no t-PA activity was detected in the plasma euglobulin fraction of endotoxin-treated animals. These data show that the thrombolytic activity of t-PA is not affected by the presence of high concentrations of circulating PAI-1.

Effects of oral contraceptives on fibrinolysis: A reassessment

Several studies have suggested an increase in t-PA activity (usually determined in euglobulin fractions of plasma) in women receiving oral contraceptives.[5-8] This was interpreted as favoring the clot-dissolving capacity of the hemostatic system. The increase in t-PA activity was apparently not caused by an increase in t-PA antigen, which, to the contrary, was significantly reduced. The explanation was assumed to be a concomitant reduction in the amount of PAI-1. A similar situation has been observed with the anabolic steroid stanozolol[23] and with respect to the afternoon increase in t-PA activity in the diurnal rhythm.[24]

However, as outlined above, measurement of t-PA

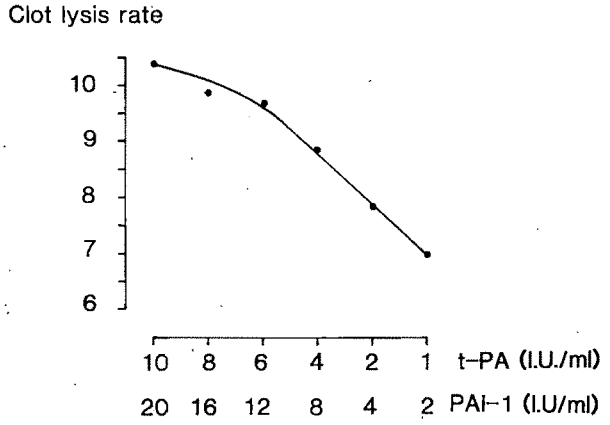


Fig. 1. Effect of decreasing amounts of PAI-1 and t-PA on plasma clot lysis rate. α_2-Antiplasmin–deficient plasma was depleted of t-PA and PAI-1 activity by prolonged incubation at 37° C. Decreasing amounts of two-chain t-PA and PAI-1 activity (from endothelial cell–conditioned medium) were added to plasma, immediately before clot formation by thrombin (final concentration, 3 NIH units/ml) and 10 mmol/L $CaCl_2$. The ratio of added PAI-1 activity to t-PA activity was 2:1 in all cases. Clot lysis rate is expressed as 1000/lysis time (in minutes). t-PA and PAI-1 activity were measured by the method of Verheijen et al.[77]

activity in plasma euglobulin fractions may not reflect the fibrinolytic capacity of t-PA in the circulation. In fact, evidence was provided that plasma fibrinolytic activity is strongly dependent on the amount of circulating t-PA rather than on PAI-1 levels. This implies that a decrease in plasma t-PA levels, as is the case in oral contraceptive users, might result in a decrease in plasma fibrinolytic activity despite a parallel decrease in PAI-1 activity. In an attempt to mimic the in vivo situation seen with oral contraceptive users, we performed a plasma clot lysis experiment in vitro, in which decreasing amounts of PAI-1 and t-PA (in a constant ratio of PAI-1 to t-PA of 2:1) were readded to plasma void of PAI-1 and t-PA activity. As shown in Fig. 1, a decrease in added t-PA resulted in a decrease in clot lysis rate despite a proportional decrease in added PAI-1 activity. This suggests that plasma fibrinolytic activity in oral contraceptive users could be diminished. It also explains why clinical studies with anabolic steroids, such as stanozolol, have not been successful in enhancing plasma fibrinolytic activity. According to these results, in the future design of an improved oral contraceptive, attention should, in our opinion, also be paid to minimizing a decrease in plasma t-PA levels.

Another reason for identifying estrogen and progestogen combinations that produce the smallest hemostatic changes is put forward by Gevers Leuven et al.[7] In a recent study on the effects of two "sub-50" oral contraceptives on plasma levels of coagulation and fibrinolysis factors, no correlations were observed between the individual changes in fibrinolytic and coagulation parameters. Thus although in both oral contraceptive–taking groups as a whole "procoagulatory" changes were stated to be balanced by "profibrinolytic" changes, in several individual cases no such compensation was seen. Therefore the use of oral contraceptives may produce individual profiles that are shifted in the direction of an increased risk of thrombosis or bleeding complications.[25] Epidemiologic data indicate that either of these disturbances occurs more frequently in oral contraceptive users than in control subjects.[26]

Molecular mechanism of steroid hormone action: The role of steroid hormone receptors and hormone response elements in the genome

Steroid hormones regulate the expression of specific genes by altering the efficiency of transcriptional initiation from their promoters. According to the "classical pathway of steroid action,"[27, 28] steroid hormone regulation of gene transcription is mediated by specific intracellular receptors in target cells, to which the hormones bind with high selectivity and affinity. On activation by hormone binding, these receptors can interact specifically with binding sites in the responsive genome, resulting in an increase or decrease in the transcription of this gene. Molecular cloning of various receptor copy deoxyribonucleic acids (cDNAs) revealed that steroid receptors are a family of hormone-dependent transcription factors having a common structural organization.[29-31] Within the steroid hormone receptor family the glucocorticoid, progesterone, mineralocorticoid, and androgen receptors are more closely related to each other in structure and function than to the estrogen receptor. The receptor protein can be divided according to sequence conservation and function into domains: an N-terminal region required for activation or repression of transcription of a gene, a central DNA-binding domain, and a C-terminal hormone-binding domain. Binding of the hormone to the receptor somehow "unmasks" the DNA-binding domain, thereby permitting specific binding to the DNA. The sites in DNA that interact with the receptor, called *h*ormone *r*esponse *e*lements (HREs), have been identified at variable distances from the promoters of a variety of steroid-regulated genes. Alignment of nucleic acid sequences in regions corresponding to identified HREs led to the definition of so-called consensus sequences (Table I). The consensus sequence for glucocorticoid response elements (GRE) and estrogen response elements (ERE) are given in Table I. No clear consensus sequence has yet been defined for progesterone, androgen, and mineralocorticoid response elements, but a GRE-15 mer is able to mediate induction by progesterone, androgens, and mineralocorticoids.[70, 71] Steroid hormone receptors

Table I. Gene regulation by steroid hormones. Consensus-responsive elements for nuclear receptors

	1	2	3	4	5	6				10	11	12	13	14	15
GRE	G	G	T	A	C	A	n*	n	n	T	G	T	T	C	T
	|	|	|	|	|	|	|	|	|	|	|	|	|	|	|
	C	C	A	T	G	T	n	n	n	A	C	A	A	G	A
ERE	A	G	G	T	C	A	n	n	n	T	G	A	C	C	T
	|	|	|	|	|	|	|	|	|	|	|	|	|	|	|
	T	C	C	A	G	T	n	n	n	A	C	T	G	G	A

A consensus sequence is derived from nucleotides conserved with a frequency of 50% or more.[30] A comparison of the available sequence information yields a 15-mer consensus sequence for the GRE and ERE.[28, 29, 32, 69, 70]

GRE, Glucocorticoid response element; *ERE,* estrogen response element.

*The n stands for A, T, G, or C.

probably bind to the HRE as a dimer. For example, the DNA contact sites of estrogen receptors display a perfect twofold rotational symmetry that is consistent with the dyad symmetry of the ERE sequence.[28] Similarly, recent results obtained by the same group of investigators indicate that glucocorticoid receptors bind to GREs as dimers.[32] It has been suggested that the hormone receptors bind to the HREs as head-to-head dimers and that binding involves a cooperative mechanism.

What can we learn from our understanding of the mechanism of steroid hormone action? From the previous discussion it is clear that the presence of specific intracellular receptors and a given motif in the gene is essential to mediate hormone-dependent regulation of gene expression. Thus we should at least make an inventory of the relevant genes of the fibrinolytic system and the cell types involved in their expression (the endothelial cells and hepatocytes as will be discussed) for the presence of HREs on the genes and steroid hormone receptors in the cells, respectively. It should be borne in mind, however, that the entire picture relating to steroid hormone regulation of gene expression cannot be explained by even the most explicit definition of receptors and primary DNA structure only. There are at least the following three complications: (1) All genes that are ever to be expressed in a given cell must be contained within an unraveled or accessible region of chromatin. (2) The same receptors do not regulate all similar sequences of expressed proteins in different cells or even in the same cell. This specificity is not yet understood. For example, MCF-7, a stable cell line of human metastatic breast cancer origin, secretes both t-PA and u-PA and both the t-PA and u-PA gene contain a sequence in their promoter region that matches the consensus ERE. On incubation with 17β-estradiol, however, increased synthesis of t-PA but not of u-PA was observed, whereas this increase in t-PA synthesis indeed appeared to be mediated by an estrogen receptor process and to require sustained ribonucleic acid (RNA) and protein synthesis.[33] (3) Hormone-induced intermediates can play a role and should be suspected when the lag period observed before the gene product rises is abnormally long. For instance, Rousseau et al.[34] found that in rat hepatoma cells, stimulation of the plasma membrane enzyme, alkaline phosphodiesterase I, by glucocorticoids requires RNA and protein synthesis but becomes detectable long after induction of tyrosine aminotransferase, a transcriptional effect, has taken place.

Identification of potential HREs in human fibrinolysis genes

We have examined the 5′-flanking DNA of the t-PA, u-PA, PAI-1, PAI-2, and α_2-antiplasmin genes for sequences similar to the consensus response elements for steroid hormone receptors. A computer search for the estrogen response element revealed sequences differing only in one or two nucleotides from the consensus sequence in all five genes (Table II). In the case of the u-PA gene, even two nearly perfectly conserved consensus sequences were found. A search for the glucocorticoid response element/progesterone response element disclosed the presence of only the most conserved hexanucleotide of the glucocorticoid response element/progesterone response element, TGTT/CCT, or its reverse complement, AGA/GACA, where A is adenine, C is cytosine, G is guanine, and T is thymine. These hexanucleotides were found repeatedly in the five genes (Table II). However, a palindromic sequence characteristic of many glucocorticoid/progesterone-responsive genes and possibly required in view of the discussed dimer-binding mechanism was not present. Whether such hexanucleotides in any of the five genes exert functions related to those of an authentic glucocorticoid response element/progesterone response element remains to be established.

Steroid hormone receptors in endothelial cells

Little is known about the presence of steroid hormone receptors in endothelial cells. Horwitz and Horwitz[35] have reported that aortas of dogs contain specific, high-affinity, low-capacity receptors for estrogens, androgens, and glucocorticoids. In addition, pro-

Table II. Putative HRE sequences in human fibrinolytic genes

ERE consensus	G	G	T	C	A		nnn		T	G	A	C	C	
Gene														Position
t-PA	*A*	G	T	C	*C*		TCA		T	G	A	C	C	−1392 to −1380
u-PA	*A*	*C*	T	C	A		GTC		T	G	T	C	C	−1691 to −1679
	G	*T*	T	C	A		AAA		T	G	A	C	C	−1342 to −1330
PAI-1	G	G	A	C	A		AGC		T	G	*C*	C	C	−879 to −867
PAI-2	G	G	T	C	A		CAT		*A*	G	A	C	*A*	−1065 to −1053
α_2-AP	G	G	T	C	A		AGG		T	G	A	C	*G*	−153 to −141
GRE/PRE consensus	T	G	T	T/C	C	T	or	A	G	A/G	A	C	A	(reverse complement)
Gene														Position
t-PA	T	G	T	T	C	T								−2340 to −2335
														−2101 to −2096
														−1504 to −1499
								A	G	A	A	C	A	−474 to −469
u-PA	T	G	T	T	C	T								−1801 to −1796
								A	G	A	A	C	A	−916 to −911
								A	G	G	A	C	A	−1149 to −1144
														−988 to −983
PAI-1								A	G	G	A	C	A	−2734 to −2729
														−880 to −875
														−297 to −292
PAI-2	T	G	T	T	C	T								−1768 to −1763
								A	G	G	A	C	A	−959 to −954
														−91 to −86
α_2-AP	T	G	T	T	C	T								−548 to −543

A computer search was performed to examine the 5′-flanking DNA of the t-PA,[72] u-PA,[73] PAI-1,[74] PAI-2,[75] and α_2-antiplasmin[76] genes for potential hormone response elements.

ERE, Estrogen response element; *GRE*, glucocorticoid response element; *PRE*, progesterone response element; *AP*, antiplasmin.

gesterone receptors could be induced by estradiol treatment. However, the receptors for the various steroid hormones are probably not in the intima because they persist when this layer is removed. Furthermore, since receptor levels were markedly lower in veins, their most likely location is in the smooth muscle of the medial layer of the artery. McGill and Sheridan[36] have investigated the presence of steroid hormone receptors in arteries from adult baboons. Of 80 sections from arteries in which endothelium could be identified, 43 (54%) had some labeled endothelial cells after injection of ^{3}H-5-α-dihydrotestosterone. Of 89 similar sections from ^{3}H-17β-estradiol–treated animals, 14 (16%) had labeling of endothelial cells. When present, endothelial cell labeling with either hormone was patchy and involved only a few contiguous cells. There was no sex difference in labeling with either hormone and in frequency of labeling among the different arteries.

Low levels of estrogen-binding sites have been found in the cytosol extracted from an endothelial cell line, which is derived from rabbit aorta endothelial cells and a rabbit fibroblast cell line.[37] Nichols et al.[38] reported the existence of classical glucocorticoid receptors in confluent bovine aorta endothelial cells but were unable to find any specific binding of [^{3}H]R1881, a potent synthetic androgen.

Steroid hormone receptors in liver cells

Estrogen. Mammalian livers of both sexes respond to sex steroid hormones. Although the human liver is not considered a classic estrogen-dependent tissue, as are the breast and uterus, it is an estrogen-responsive organ. Estrogen administration is known to alter several hepatic functions in humans (both men and women), ranging from increased secretion of many serum transport proteins to alterations in drug metabolism.[39] High-affinity, low-capacity, estrogen-specific binding proteins have been identified in the livers of several mammals including man, which suggests that the hormone may exert a direct effect on the tissue.[39-41]

Tam et al.[42] have looked for estrogen receptors in the hepatocarcinoma cell line, Hep G2. When Hep G2 cells are cultured in medium that is not supplemented with estrogen, they contain very low levels of estrogen-specific binding sites in both nuclear and cytosolic fractions. When the cells are exposed to hormone, the levels of nuclear sites increase markedly. Two nuclear-binding components can be distinguished: a high-affinity component, with a dissociation constant (K_d) for 17β-estradiol comparable with that of mammalian type I estrogen receptor and a lower affinity component, whose dissociation constant is similar to that of the type

II binding sites reported to be present in rat uterine nuclei.[43] Testosterone induces a cytoplasmic moderate-affinity, estrogen-binding component in Hep G2 cells.[44] This component may function as an estrogen "sink," which results in an increase in estrogen concentrations required for maximal induction of, for example, different apolipoproteins in Hep G2 cells.

Androgen. Male livers are strikingly androgen responsive. At first, many investigators failed to demonstrate the presence of intracellular androgen receptors, but subsequently using improved assay procedures, they were unequivocally identified.[45] Maintenance of the androgen receptor apparently requires the presence of relatively high serum concentrations of androgen, since castration of the male (rats) results in a time-dependent loss of both cytosol and nuclear receptors.[46] In accordance with this mechanism, androgen-binding activity is low in livers from females, but can be induced by testosterone treatment. As argued by Mooradian et al.,[47] many effects of androgens on liver are probably mediated by receptor-dependent mechanisms, but others are elicited directly by androgens, with the cooperation of hormones from the anterior pituitary, especially somatotropin and somatostatin.

Recently Tam et al.[44] provided evidence of the presence of high-affinity androgen receptors in the human hepatoma cell line Hep G2.

Progesterone. Several investigators have searched for progesterone receptors in liver. For example, Conneely et al.[48] used a chicken progesterone receptor cDNA probe for Northern blot analysis of total cellular RNA obtained from the livers of estrogen-treated chicks, but no detectable progesterone receptor messenger RNA (mRNA) was found. Expression of the receptor gene appeared to be highly specific for the oviduct.

Glucocorticoids. In contrast to sex hormones, which are limited in their ranges of target tissues, there are probably only a few cell types that do not respond in one way or another to glucocorticoids.[49, 50] Hepatic cells are among the major targets for glucocorticoids.[49, 51] As far as we know today, all direct effects of glucocorticoids on cells are mediated through the glucocorticoid receptor.[49, 50]

Cultured human endothelial cells and human hepatocytes as an in vitro model system to study regulation of t-PA and PAI-1 synthesis

We have examined the possibility of using cultured human endothelial cells and the human hepatoma cell line Hep G2 as an in vitro model to investigate molecular mechanisms underlying the cellular responses to steroid hormones. The t-PA in the blood stream is presumed to be derived from the vascular wall, where it is localized in the endothelial cells.[52] Although the cellular origin of plasma PAI-1 is still unknown and a contribution of other body cells cannot be excluded, we have used endothelial cells and hepatocytes as a model system to study regulation of PAI-1 synthesis. The validity of this model can be illustrated by the effects of endotoxin, cytokines, and insulin on the synthesis of PAI-1. PAI-1 in plasma behaves as an acute-phase reactant: a rapid increase in PAI-1 activity is seen after major surgery, severe trauma, and myocardial infarction.[53] In addition, PAI-1 activity can be induced in rats by intravenous injection of endotoxin or the acute phase mediators, interleukin-1, and tumor necrosis factor.[54, 55] Another example of altered PAI-1 levels in plasma has come from a study by Juhan-Vague et al.[56]: they showed a close correlation between plasma insulin levels and plasma PAI-1 levels. Both in vivo effects can be mimicked in our in vitro system. The addition of endotoxin, interleukin-1, or tumor necrosis factor to the culture medium stimulated the production of PAI-1 by endothelial cells from umbilical vein and foreskin microvessels several fold.[54, 55] On the other hand, insulin increased fairly specifically PAI-1 synthesis in Hep G2[57] and in primary cultures of human hepatocytes.[58]

Compared with the standard incubation protocol, the testing of steroid hormones in our model required some extra precautions: (1) Phenol red, which is used ubiquitously as a pH indicator in tissue culture media, bears a structural resemblance to some nonsteroidal estrogens and has significant estrogenic activity at the concentrations (15 to 45 μmol/L), at which it is found in tissue culture media.[59] Phenol red binds to the estrogen receptor of MCF-7 human breast cancer cells with an affinity 0.001% that of estradiol ($K_d = 2 \times 10^{-5}$ mol/L). Cells used in our studies were therefore cultured and maintained in culture media void of indicator. (2) Maintenance of Hep G2 cells in a wide range of estradiol concentrations indicated that adjustment of the medium to 20 nmol/L in hormone every 12 hours was adequate to maintain nuclear binding at 90% of the maximal levels obtainable.[42] This is considerably higher (about 20-fold) than peak circulating concentrations of estradiol found in premenopausal nonpregnant women, but since hepatocytes metabolize the hormone extremely rapidly ($t_{1/2}$ = 1 hour), the effective steady-state concentrations of the hormone in the culture system are likely to be considerably lower. Consequently, it is not possible to equate the nominal concentrations in the cultures with circulating in vivo levels. (3) When Hep G2 cells are cultured in medium that is not supplemented with estrogen, they contain very low levels of estrogen-specific binding sites in both nuclear

Table III. Effect of steroid hormones on the production of t-PA and PAI-1 by cultured human endothelial cells and Hep G2 cells

	Endothelial cell CM		*Hep G2 CM*
Hormone added	*t-PA*	*PAI-1*	*PAI-1*
Estradiol	96% ± 2%	110% ± 4%	103% ± 2%
Ethinyl estradiol	94% ± 4%	105% ± 1%	101% ± 2%
Testosterone	103% ± 7%	106% ± 1%	101% ± 6%
Methyltestosterone	111% ± 9%	98% ± 2%	97% ± 6%
Progesterone	94% ± 4%	93% ± 5%	108% ± 7%
Levonorgestrel	97% ± 5%	111% ± 7%	106% ± 5%
Gestodene	95% ± 2%	105% ± 1%	103% ± 4%

CM, Conditioned media.

Endothelial cells from human umbilical veins (only female vessels were used) were isolated and cultured as previously described.[55] Conditioned media were obtained by incubating second-passage, confluent cells at 37° C for 3 consecutive periods of 24 hours in M199-medium (indicator-free), supplemented with 10% (v/v) human serum, 20 mmol/L HEPES, glutamine, penicillin, streptomycin, 0.01% (v/v) ethanol, and with or without hormone (10^{-9}, 10^{-8}, or 10^{-7} mol/L). Every 24 hours, conditioned media were collected and fresh medium was added to the cells. Conditioned media were immediately centrifuged (to remove cellular debris) and stored at −20° C.

The cell line Hep G2 was subcultured and grown as previously described.[58] To obtain conditioned media, cells were grown to about 50% confluency and incubated at 37° C in minimum essential medium Eagle with Earle's salts (EMEM) (indicator-free), which was supplemented with 10% (v/v) fetal bovine serum, glutamine, penicillin, streptomycin, 0.01% (v/v) ethanol, and with or without hormone (10^{-8}, 10^{-7}, or 10^{-6} mol/L), exactly according to the protocol described above for endothelial cells. Each experiment was performed with incubations in duplicate. The t-PA antigen levels were assayed by enzyme immunoassay (Biopool, Umeå, Sweden). PAI-1 activity was measured by the method of Verheijen et al.[77] Values were expressed as percentage values relative to control values. The data shown represent means ± range of two separate experiments, after 72 hours of incubation in the presence of 10^{-7} mol/L (endothelial cells), or 10^{-6} mol/L (Hep G2) hormone.

and cytosolic fractions. A high-affinity binding component increased relatively rapidly to reach approximately 50% and 80% of the 48-hour level within 3 and 8 hours, respectively, after initial exposure to 20 nmol/L of the hormone.[60] In contrast, induction of a low-affinity component had a lag of several hours and only reached 10% of the 48-hour level 8 hours after the addition of hormone. Thereafter it accumulated rapidly to 90% of the 48-hour level within 24 hours. The increase in the level of high-affinity nuclear estrogen binding sites was accompanied by an increase in the levels of apolipoprotein-A_1 mRNA and secreted protein. New steady-state levels of apolipoprotein-A_1 mRNA and the rate of apolipoprotein-A_1 protein synthesis, approximately twice those of control cultures, were established within 24 to 48 hours of exposure to 17β-estradiol. These increases in apolipoprotein-A_1 levels were obtained when estradiol was added either to dividing cells or to cultures that had just reached confluency.[42] However, a decreased response was observed in cells that had been confluent for periods beyond 24 hours before hormone treatment. In our protocol, Hep G2 cells were grown to 50% confluency before hormone was added to the medium. The incubation medium was refreshed every 24 hours for 3 days. Usually cells reached confluency after 2 days. (4) Seillan et al.[61] studied the effect of testosterone (10^{-8} mol/L) and 17β-estradiol (10^{-8} mol/L) on the secretion of prostaglandins (I_2, E_2, and $F_{2\alpha}$) by cultured endothelial cells from male and female piglets. After 5 days of incubation, cells from female aortas responded to testosterone and 17β-estradiol by a marked increase in prostaglandin secretion (three to five times), whereas endothelial cells from male animals were insensitive to androgen and estrogen. In addition, in male cells no steroid degradation was observed, whereas in female cells, both testosterone and estradiol were partially metabolized. Therefore in our experiments we used only endothelial cells from female umbilical veins. In this respect, it should be noted that the Hep G2 cell line was established from a liver tumor biopsy of a boy.[62]

Effect of steroid hormones on the production of t-PA and PAI-1 in cultured endothelial cells and hepatocytes

We have cultured endothelial cells and Hep G2 cells for periods up to 72 hours in the presence of maximally 10^{-7} and 10^{-6} mol/L steroid hormone, respectively. Under these conditions, 17β-estradiol has been reported to stimulate endothelial cells to increase their production of von Willebrand factor about 1.7 times, albeit that estradiol also caused a slight increase in cell replication.[63] Similarly, 17β-estradiol increased apolipoprotein A_1 synthesis in Hep G2 about twofold.[42, 44, 60] However, as shown in Table III, none of the hormones tested, that is, estradiol, ethinyl estradiol, testosterone, methyltestosterone, progesterone, levonorgestrel, and gestodene, showed a significant effect on the production of t-PA or PAI-1 in either cell type. Comparable results were obtained at shorter incubation periods (24

or 48 hours), at lower hormone concentrations, or when PAI-1 antigen (Biopool Imulyse PAI-1 assay) rather than PAI-1 activity was measured (results not shown). In several cases, hormones were tested at lower serum concentrations (1%), or subconfluent cultures of endothelial cells were used but without effect. Maintaining endothelial cells or Hep G2 in the presence of hormone had no detectable effect on their viability compared with control cultures.

Our results indicate that cultured endothelial cells and Hep G2 cells cannot easily be used as a model system to study the effect of pill components on the synthesis of fibrinolytic variables in vitro. A similar experience was obtained in testing stanozolol in our in vitro model (unpublished results).

Several concluding remarks are to be made. Evidence is provided that the fibrinolytic capacity in plasma is dependent on circulating t-PA levels rather than on PAI-1 activity. The view that the reported decrease in plasma t-PA protein after oral contraceptive use is compensated by the concomitant decrease in PAI-1 level is questioned. It is argued on both theoretic and experimental grounds that a decrease in plasma t-PA levels as observed in oral contraceptive users is associated with a decrease in plasma fibrinolytic capacity. For future design of an improved oral contraceptive, maintenance of normal plasma t-PA levels should be pursued if possible.

In the second part of this article, studies on the mechanism of action of oral contraceptives at the cellular level are reviewed. It is now clear that the presence of a given motif in a gene and the presence of a specific intracellular receptor can mediate hormone-dependent regulation of gene expression. A computer search revealed potential estrogen response elements in the t-PA, u-PA, PAI-1, PAI-2, and α_2-antiplasmin genes. Because we assumed that endothelial cells and hepatocytes are the main sources of plasma fibrinolytic components, we have searched the literature for the presence of steroid hormone receptors in these cells. In contrast to glucocorticoid receptors, no convincing evidence for the presence of sex steroid receptors in endothelial cells was found. In addition to glucocorticoid receptors, liver cells clearly contain estrogen receptors (in both male and female cells) and androgen receptors (normally in male cells, but inducible in female cells), whereas no progesterone receptors in these cells could be detected. These data suggest the possibility that PAI-1 synthesis in hepatocytes (these cells do not produce t-PA) is regulated by estradiol by way of a receptor-mediate pathway and an estrogen response element in the PAI-1 gene. However, this possibility is not supported by our in vitro experiments: Hep G2 cells did not respond to estradiol or ethinyl estradiol with respect to PAI-1 synthesis. In fact, neither endothelial cells nor Hep G2 cells showed a change in t-PA or PAI-1 synthesis on addition of any of the hormones tested. Therefore our in vitro model system provides no evidence for diminished synthesis of t-PA and PAI-1 as a direct effect of the hormones.

The plasma level of a molecule is the result of two processes, influx and clearance. Thus an alternative way in which oral contraceptive components could reduce plasma levels of t-PA and PAI-1 would be an increase in the clearance rate of both proteins, for example, by an increase in the number of receptors. Indeed, several studies report that the number of cell surface receptors for a ligand can be under hormonal control. Poola and Lucas[64] found that the oviduct has an estrogen-inducible transferrin receptor. Estrogen has also been shown to enhance the number of low-density lipoprotein receptors present on rabbit hepatocytes[65] and Hep G2 cells[66] and to enhance epidermal growth factor receptors in rat uterine.[67] Treatment of postmenopausal women with low doses of 17β-estradiol and *dl*-norgestrel significantly lowered very low–density lipoprotein triglycerides in four of five subjects by enhancing their clearance.[68] It is likely that as a greater number of systems are studied, estrogen and perhaps other steroid hormones, will be found to play a significant role in regulating a number of cell surface receptors. Whether these receptors will include receptors for t-PA or PAI-1 remains to be established.

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Metabolic changes during the normal menstrual cycle: A longitudinal study

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The effect of sex hormones on lipid metabolism and coagulation during the menstrual cycle was studied in 37 women. Each woman had three samples drawn, corresponding to the follicular phase, midcycle, and the luteal phase. Basal conditions were obtained by taking samples in the morning while subjects were still in bed. No changes were found in lipids and lipoproteins during the menstrual cycle. Antithrombin III and factor VII of the coagulation system did not change throughout the cycle. Fibrinogen increased in the luteal phase, and all samples of fibrinogen correlated positively with progesterone concentration. This increase, therefore, could be a progesterogenic effect. In conclusion, these findings suggest that when studied optimally no changes in lipids and lipoproteins are found and that the day of blood samples is of minor importance, for instance, when used as a control in studies of oral contraceptives. For investigations on some coagulation parameters, the days of the cycle may be of importance. (Am J Obstet Gynecol 1990;163:414-6.)

Key words: Menstrual cycle, lipid metabolism, blood coagulation

Sex hormones influence lipid metabolism and produce changes in the coagulation system. Several studies have been undertaken in women taking oral contraceptives, but in addition, it would be of interest to investigate if the changes in sex hormones seen during the normal menstrual cycle could induce changes in lipids and coagulation.

In this study we investigated possible changes in some coagulation parameters and lipids and lipoproteins, including the high-density lipoprotein 2 (HDL_2) fraction and apolipoproteins.

Material and methods

Thirty-seven apparently healthy, nonobese women took part in this study. Their median age was 25 years (range, 19 to 36 years). All had regular menstrual cycles (25 to 36 days).

Blood samples were drawn three times during the cycle: days 6 to 8 (follicular phase), days 12 to 14 (midcycle), and days 24 to 26 (luteal phase). Samples were taken in the morning while subjects were still in bed at home. Blood samples were spun and serum or plasma withdrawn.

The following hormones were measured by radioimmunoassay: 17β-estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, and prolactin.

Triglyceride and total cholesterol levels were determined by enzymatic methods with commercial kits (Boehring, Federal Republic of Germany). High-density lipoprotein cholesterol was determined in the supernate after precipitation of apolipoprotein B–containing lipoprotein with phoshotungstate/magnesium^{2+}.[1] Low-density lipoprotein cholesterol was determined indirectly by means of the Friedewald formula.[2] Determination of HDL_2 was done by a modification of a two-step precipitation method.[3] Apolipoproteins were measured by electroimmunoassay in agarose gel.

Antithrombin III was assessed functionally,[4] factor VII by a commercial kit (Dade AG, CH), and fibrinogen by coagulimetry as the difference in diffused light.

Statistical evaluation was performed with analysis of variance followed by Duncan's test. Correlation was expressed by Pearson's r, and $p < 0.05$ was chosen as level of significance.

Results

Table I presents the serum levels of hormones. 17β-Estradiol was three to four times higher at midcycle (days 12 to 14) and two to three times higher in the luteal phase (days 24 to 26) than in the follicular phase (days 6 to 8). Progesterone was 10 to 15 times higher in the luteal phase than in the follicular phase or at midcycle. Follicle-stimulating hormone decreased in the luteal phase, and luteinizing hormone showed a maximum at midcycle. Prolactin did not change through the cycle.

Results of the lipid parameters are shown in Table II. None of the serum lipids, lipoproteins, or apolipoproteins changed throughout the cycle.

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Table I. Serum concentration of 17β-estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, and prolactin during the menstrual cycle (mean ± SEM; $n = 37$)

	Cycle days		
	6-8, follicular phase	*10-12, midcycle*	*24-26, luteal phase*
17β-estradiol (nmol/L)	0.20 ± 0.01	0.70 ± 0.07***	0.54 ± 0.03***
Progresterone (nmol/L)	2.93 ± 0.23	3.17 ± 0.31	39.8 ± 3.20***†††
Luteinizing hormone (IU/L)	10.4 ± 0.89†	18.2 ± 3.80*	8.38 ± 1.04†
Follicle-stimulating hormone (IU/L)	6.70 ± 0.58	5.92 ± 0.68	2.87 ± 0.22**††
Prolactin (mIU/L)	799 ± 68.7	683 ± 40.5	806 ± 83.0

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ vs days 6 to 8.
†$p < 0.05$, ††$p < 0.01$, and †††$p < 0.001$ vs days 10 to 12.

Table II. Lipid concentrations and apolipoprotein levels during the menstrual cycle (mean ± SEM)

	Cycle days		
	6-8, follicular phase	*10-12, midcycle*	*24-26, luteal phase*
Triglycerides (mmol/L)	0.89 ± 0.06	0.93 ± 0.07	0.93 ± 0.07
Total cholesterol (mmol/L)	4.61 ± 0.15	4.58 ± 0.17	4.34 ± 0.16
LDL cholesterol (mmol/L)	2.81 ± 0.14	2.78 ± 0.15	2.58 ± 0.13
HDL cholesterol (mmol/L)	1.71 ± 0.08	1.70 ± 0.08	1.61 ± 0.07
HDL_2 cholesterol (mmol/L)	0.48 ± 0.06	0.52 ± 0.05	0.42 ± 0.06
Apolipoprotein A_1 (gm/L)	1.20 ± 0.03	1.18 ± 0.03	1.19 ± 0.03
Apolipoprotein B (gm/L)	0.87 ± 0.04	0.87 ± 0.04	0.84 ± 0.04

LDL, Low-density lipoprotein; *HDL,* high-density lipoprotein.

Table III. Plasma concentration of antithrombin III, factor VII, and fibrinogen in the menstrual cycle (mean ± SEM)

	Cycle days		
	6-8, follicular phase	*10-12, midcycle*	*24-26, luteal phase*
Antithrombin III (%)	106.4 ± 2.3	106.3 ± 1.7	107.5 ± 1.8
Factor VII (%)	117.2 ± 7.8	104.3 ± 5.4	98.1 ± 5.0
Fibrinogen (nmol/L)	7.30 ± 0.29	7.29 ± 0.23	8.18 ± 0.28*†

*$p < 0.05$ vs days 6 to 8.
†$p < 0.05$ vs days 10 to 12.

Table III shows antithrombin III, factor VII, and fibrinogen values. Only fibrinogen showed a change. A 12% increase was found in the luteal phase when compared with the follicular phase and midcycle. Fibrinogen concentrations correlated positively with progesterone concentrations ($n = 108$; $r = 0.28$; $p < 0.01$).

Comment

Hormone values show results confirming that the samples were drawn in the follicular phase, at midcycle, and in the luteal phase. Total cholesterol and triglyceride values did not change in our study, which is in agreement with Demacker et al.[5] However, according to Kim and Kalkhoff[6] and Adlercreutz and Tallqvist,[7] changes were found. These differences could be explained on the basis of the larger number of women and the longitudinal design of our study.

High-density lipoprotein and low-density lipoprotein cholesterol did not fluctuate throughout the cycle, which is inconsistent with Hemer et al.[8] and Demacker et al.[5] Other authors have found changes in high-density lipoprotein and low-density lipoprotein cholesterol throughout the cycle.[9] This discrepancy could apart from the larger group and longitudinal design of our study be explained by the optimized blood collection procedure that consisted of drawing the samples early in the morning and before subjects got out of bed; confirmation of basal conditions is the high prolactin levels resulting from sleep-associated augmentation.[10] HDL_2 cholesterol has, as far as we know, not been previously measured in the normal menstrual cycle. This interesting subfraction in respect to cardiovascular disease did not change nor did apolipoprotein A_1, which is its main carrier protein. The changes in sex hormones are probably of too short duration to affect the liver's metabolism of lipoproteins, and this

could explain the absence of changes found in lipids.

However, fibrinogen, which is also produced in the liver, rose in the luteal phase, which seems to be a progesterogenic effect according to the positive correlation found. Antithrombin III did not change throughout the cycle. Some authors, however, have found minor changes.[11]

In conclusion, we found that if a longitudinal study performed under optimal conditions on a large group of women is made, no changes in lipids and lipoproteins can be found throughout the menstrual cycle. Therefore the day of the cycle on which blood samples are drawn, for instance, as control values, in studies of lipid metabolism in women taking oral contraceptives seems to be of minor importance. When coagulation is studied, the day may be of some importance for some variables.

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Influence of oral contraceptives on coagulation tests in native blood and plasma

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Routine coagulation laboratory tests, clotting times in native (not anticoagulated) whole blood, platelet-rich and platelet-poor plasma, and recalcification times in citrated whole blood, platelet-rich and platelet-poor plasma were performed in 14 healthy premenopausal women. Blood was taken before and after one or two cycles of low-dose oral contraceptives. After oral contraceptives a reduction in clotting time in native platelet-rich plasma and activated partial thromboplastin time were observed. Recalcification times in whole blood and platelet-rich plasma were shorter than clotting times in their native counterparts. The observed changes are compatible with a procoagulant effect seen soon after the start of oral contraceptive use. The absence of these changes in the recalcification times in citrate systems suggests a masking effect of citrate. The reduction in clotting times in native platelet-rich but not in platelet-poor plasma indicates that the hypercoagulability in oral contraceptives users is mainly related to platelets. (AM J OBSTET GYNECOL 1990;163:417-20.)

Key words: Oral contraceptives, coagulation, native blood, activated partial thromboplastin time

There is a vast body of literature on changes in blood coagulation in users of oral contraceptives (OCs) and the induction of a hypercoagulable state, which is defined as procoagulatory changes in some coagulation tests (accelerated clotting or changes in clotting factors or inhibitors).[1-5] Much of the published data is conflicting, which partly reflects technical differences in the assay systems, as well as problems in an accurate diagnosis of deep vein thrombosis.[6,7] The insufficient reliability of epidemiologic data reporting an association between OC use and deep vein thrombosis has been discussed extensively.[8]

There is also no consensus on the relevance of the reported hemostaseologic findings, for example, a decrease in antithrombin III or a rise in fibrinogen concentration.[9] On the other hand, divergent effects may compensate each other, as may be the case with reported procoagulatory and profibrinolytic effects.[10]

To date there is no coagulation laboratory test available for assessment of individual thromboembolic risk.

In our laboratory we developed clotting tests in native (i.e., not anticoagulated) blood and plasma, which revealed hypercoagulability in coronary heart disease and diabetes mellitus (unpublished data) not disclosed by the conventional citrate test systems. This prompted us to examine, with these test systems, the effects of low-dose OC use on blood coagulation, with test persons serving as their own control.

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Material and methods

Fourteen healthy women taking no other medication (particularly no medication known to influence coagulation or platelet function for at least 14 days) participated after they gave informed consent. All used low-dose OC formulations (containing ethinyl estradiol, 0.03 mg in 13 patients and 0.04 mg in 1 patient). They were examined in the second half of the menstrual cycle before and between the eighteenth and twenty-first day of the first (nine women) or second (five women) cycle of OC use.

All clotting time measurements were performed in duplicate on a hook coagulometer (Amelung, Lemgo, West Germany) at 37° C. Blood was obtained by atraumatic puncture of an antecubital vein through a 1.2-gauge needle. In citrated samples 9 volumes of blood were mixed with 1 volume of 0.11 mol/L sodium citrate (Sarstedt tubes, Vienna, Austria).

Immediately after blood collection, 0.3 ml of native whole blood was transferred to the coagulometer, and clotting time was recorded.

The preparation of native platelet-rich and native platelet-poor plasma was carried out at 4° to 10° C by differential centrifugation (5 minutes at 400 *g* for native platelet-rich plasma; 10 minutes at 2000 *g* for native platelet-poor plasma). Cooling is essential to prevent coagulation. Contact with glass surfaces was avoided. Native platelet-rich plasma was adjusted to a platelet

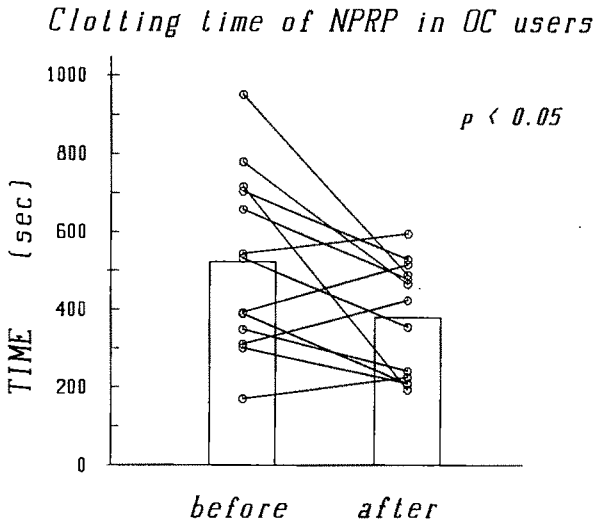


Fig. 1. Clotting times in native platelet-rich plasma *(NPRP)* before and after OC use. *Bars* denote the means of 13 values. (Data are missing in 1 of 14 cases.)

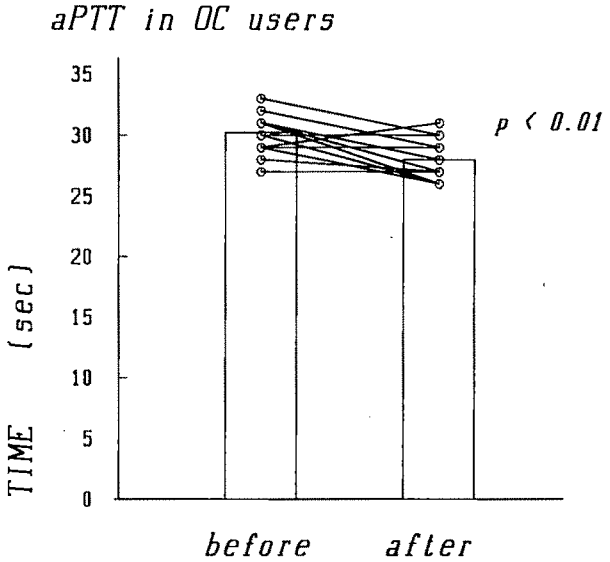


Fig. 2. Activated partial thromboplastin time *(aPTT)* (in citrated plasma) before and after OC use. *Bars* denote the means of 14 values. Some points and lines are overlapping.

concentration of 250 G/L by addition of autologous native platelet-poor plasma. Clotting times were recorded in 0.3 ml samples.

In the citrated systems, recalcification times in 0.2 ml samples were recorded after the addition of 0.2 ml of 0.025 mol/L $CaCl_2$.

A platelet count was performed on a Coulter counter in whole blood, platelet-poor plasma, and before and after adjustment of the platelet concentration in platelet-rich plasma (both in native and citrated samples).

Routine coagulation tests were performed on citrated blood or plasma, according to the instructions of the manufacturers: activated partial thromboplastin time (cephaloplastin Dade, Merz + Dade, Düdingen, Switzerland), partial thromboplastin (Boehringer, Mannheim, West Germany), fibrinogen,[11] antithrombin III (Boehringer), and thrombelastography[12] (Hellige thrombelastograph D, Freiburg, West Germany). A blood count was carried out on a Coulter counter.

The Wilcoxon matched-pairs signed-ranks test was used to test for statistically significant differences; correlations were tested according to standard nonparametric procedures. BMDP statistical package subprograms 3D and 8D, respectively, (BMDP statistical software, Inc., Los Angeles, Calif.) were applied.

Results

A significant reduction in clotting times was observed in native platelet-rich plasma (Fig. 1) and activated partial thromboplastin time (Fig. 2) after OC use but not in the other test systems (Table I). Neither the increase in fibrinogen concentration nor the decrease in antithrombin III was statistically significant (Table I).

Clotting times in native whole blood and platelet-rich plasma were significantly longer than in their citrate counterparts before OCs ($p < 0.01$; Table I); after OCs only the whole blood methods differed significantly ($p < 0.05$; Table I).

Platelet counts in native and citrated platelet-rich plasma before adjustment to 250 G/L did not differ significantly (339 ± 112 vs 348 ± 82 G/L).

Coagulation test changes did not differ between first and second cycle. No correlation was observed between changes in clotting times of native platelet-rich plasma and activated partial thromboplastin time.

Comment

There is still ongoing debate on whether OC use induces the development of hypercoagulability or increases the risk of deep venous thrombosis, especially if the newer low-dose formulations are used. The establishment of a correlation between OC use and clinically manifest thromboembolic disease is confounded by a rather high rate of false-positive and false-negative errors in clinical diagnosis. However, clinical experience suggests an influence of OC use, because in young women deep vein thrombosis appears to occur almost exclusively in OC users or in very obese persons. In an ongoing study at our clinic, 24 of 37 premenopausal women with deep vein thrombosis received OCs (prevalence of OC use in our area is 25%); of the remaining 13 women, 8 were obese.

The most commonly reported blood coagulation alterations in OC users are a decrease in antithrombin III and an increase in platelet aggregability and fibrinogen, all compatible with a shift to hypercoagula-

Table I. Mean ± SD of the tested variables before and after OC use

Clotting times	*Before*	*After*	*Unit of measure*	*p value*
	Mean ± SD	*Mean ± SD*		
Native				
Whole blood	409.0 ± 155.4	364.9 ± 128.4	sec	
Platelet-rich plasma	521.9 ± 227.9	378.0 ± 145.7	sec	<0.05
Platelet-poor plasma	1052.5 ± 734.3	974.2 ± 689.1	sec	
Citrate				
Whole blood	264.4 ± 50.3	279.8 ± 114.3	sec	
Platelet-rich plasma	385.3 ± 152.9	346.6 ± 149.2	sec	
Platelet-poor plasma	715.4 ± 579.3	779.0 ± 639.6	sec	
aPTT	30.2 ± 1.7	28.0 ± 1.7	sec	<0.01
Other coagulation tests				
Platelets	237.5 ± 34.6	223.5 ± 43.7	gm/L	
Prothrombin time	91.6 ± 21.5	92.9 ± 9.0	%	
Fibrinogen	249.3 ± 56.2	278.8 ± 63.1	mg/dl	
Antithrombin III	106.6 ± 16.4	96.9 ± 11.4	%	
Thrombelastography r*	8.1 ± 2.9	7.9 ± 1.9	min	
Thrombelastography k*	5.8 ± 2.1	6.0 ± 2.1	min	
Thrombelastography ma*	50.1 ± 7.0	51.2 ± 4.6	mm	

*The thrombelastography parameters are[12]: *r*, reaction time; *k*, thrombus formation time; *ma*, maximal amplitude.

bility.[3-5, 8] However, not all investigations confirmed these results[15]; in our study the lack of significant differences might be because of the small number of patients. On the other hand, several papers[9, 14] report an increase in fibrinolytic activity, which may compensate for procoagulant changes.

The significant shortening of clotting time in native platelet-rich plasma but not in the other native test systems observed in our study suggests a role of platelets in mediating the effects of OCs. An increase in platelet activation has been described in other reports, however, not unanimously.[2]

The additional influence of erythrocytes[15] is probably the main reason why these changes between before and after OC use were not seen in whole blood. Another reason might be activation of platelets and/or coagulation by cooling; this, however, appears to be of minor relevance, because in uncooled citrate the clotting time of platelet-rich plasma was shorter than in cooled native platelet-rich plasma.

The lack of differences in recalcification times in the citrate systems before and after OC use points to a masking effect of citrate, probably because of a platelet-aggregating effect. This is in agreement with results of another study[15] in native blood in which a sex difference in platelet aggregation with stronger platelet aggregation responses in women, not detectable in citrate, was observed. The differences between native and citrate systems may be caused by altered platelet function as a consequence of reduction as well as Ca^{2+} availability of increased pH in citrate.[16, 17] Since the platelet concentration before adjustment to 250 G/L was the same in native and citrate platelet-rich plasma, a different platelet distribution can be ruled out as the reason for the differences between native and citrate systems.

As illustrated in Figs. 1 and 2, the decrease in clotting time was not uniformly observed in all subjects, which indicates differing individual reactions. Moreover, changes in the same persons were not unidirectional in native platelet-rich plasma and activated partial thromboplastin time, which is not surprising, since partly different phases of coagulation were tested.

The observed reduction of activated partial thromboplastin time has also been reported by some other groups,[2, 14, 18] which suggests changes in intrinsic plasma coagulation factors in OC users, for example, increased factor XII concentration.[9]

One of the several reviews[8] on the subject came to the conclusion that "at this time, it is not known whether oral contraceptives do or do not trigger the hemostasis system to develop a thrombosis or by which mechanism they could trigger the event." Our data speak in favor of an effect of OC use (including the low-dose formulations) on blood coagulation, with a shift toward faster clotting demonstrable after one to two pill cycles. This seems to be mediated at least in part by increased reactivity of blood platelets, which is detectable in native but not in citrate blood.

The impact of the type of sex steroids used and other cofactors (e.g., smoking) needs further study. Whether the detected changes will still be observed after a longer period of OC use still needs to be determined.

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Hemostasis profile in women taking low-dose oral contraceptives

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Thirty-six young, healthy, nonsmoking women have been selected to check the effect of low-dose oral contraceptives on hemostasis. Two identical groups were treated by Marvelon (a monophasic oral contraceptive containing ethinyl estradiol and desogestrel) or Trigynon (a triphasic oral contraceptive containing ethilyl estradiol and levonorgestrel) for a 6-month period. In the absence, previously controlled, of substantial differences between the effects of each treatment on hemostasis, all the results were pooled at the third and sixth month of the study. The effects of oral contraceptive treatment were as follows: (1) platelet number, platelet aggregating ratio, and plasma β-thromboglobulin level were not significantly altered, and (2) antithrombin III activity was not reduced despite a slight decrease or antigen concentration. The von Willebrand factor parameters, factor VIII:C, factor VII:C, and clottable fibrinogen were significantly increased. Plasminogen (activity and antigen concentrates) and α_2-antiplasmin levels were also significantly increased. Activated partial thromboplastin time and euglobulin lysis time measured after venous occlusion were significantly shortened. Although statistical analysis did not show dramatic changes in all these parameters, some individual extreme values were substantially altered. Therefore we believe that these later values are worthy of cautious consideration for weighing the role that hemostasis factors might play in individual thrombotic risk. (AM J OBSTET GYNECOL 1990;163:420-3.)

Key words: Oral contraception, platelets, von Willebrand factor, coagulation, fibrinolysis

Despite an overall reduction of thrombotic events in users of low-dose oral contraceptives, recent epidemiologic data are consistent with an increased risk of deep venous thrombosis and pulmonary embolism in treated women.[1] The thrombotic risk linked to oral contraceptive use is probably multifactorial, involving diverse alterations in hemostasis.[2] It is generally accepted that these later alterations are induced by the estrogen component of oral contraceptives and are dose related.[3,4] The estrogenic effect may be under a modulating influence of progestogens.

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According to several recent studies, no dramatic changes in the hemostatic profile were observed in selected women treated by low-dose oral contraceptives, although some significant modifications of coagulation and fibrinolysis have been reported.[5, 6] However, we wondered whether some individual values of hemostasis variables could not have reached a level largely beyond the usually accepted reference range. Such individual alterations on hemostasis should be noticed, taking into account that epidemiologic studies have shown a positive correlation between the thrombotic risk and the level of fibrinogen and factor VII:C.[2]

Therefore in this study, we have considered not only the statistical dispersion but also the extreme values of parameters such as platelets, von Willebrand factor, coagulation, and fibrinolysis tested in a homogeneous cohort of 36 young healthy, nonsmoking women. This cohort was divided in two groups, each of whom received for 6 months one of two widely used low dose preparations, Marvelon (mono-DG), a monophasic oral contraceptive containing ethinyl estradiol (30 mg) and desogestrel (150 mg), and Trigynon (trilevonorgestrel), a triphasic oral contraceptive containing ethinyl estradiol and levonorgestrel (6 days ethinyl estradiol, 30 mg + levonorgestrel, 50 mg; 5 days ethinyl estradiol, 40 mg + levonorgestrel, 75 mg; 10 days ethinyl estradiol, 30 mg + levonorgestrel, 125 mg).

In this article, the results of both groups have been pooled after we observed that there was no substantial difference between the effects of each preparation on hemostasis.

Material and methods

Thirty-six women between 21 and 34 years of age were nonsmoking healthy volunteers. Some had stopped oral contraceptives for at least 8 weeks before the study, and the others had never used oral contraceptives. These women were treated with Marvelon (mono-DG group) or Trigynon (tri-LNG group). The use of aspirin or of other nonsteroidal antiinflammatory drugs was avoided during the study. A hemostatic control was performed during the last untreated cycle, 7 days before presumed menstruation. The oral contraceptive treatment was continued for six cycles. Hemostatic controls were performed between days 18 and 21 of the third and sixth months of treatment. Thus each woman served as her own control.

Venous samples of blood were taken in fasting women at rest. Platelets were enumerated by a Coulter counter. Platelet aggregate ratio was computed by counting free platelets on whole blood sample, which gave an index of circulating aggregates.[7] Plasma β-thromboglobulin was measured by radioimmunoassay after suitable blood sampling.[8] The von Willebrand factor was evaluated by its related antigen (vWF:Ag) measured by electroimmunodiffusion[9] and by its ristocetin cofactor activity.[10] Activated partial thromboplastin time, clottable fibrinogen, factor VIII:C, and factor VII:C were determined according to the principles of routine techniques. Antigenic levels of antithrombin III and plasminogen were determined by radioimmunodiffusion with plates purchased from Behring. Antithrombin III, plasminogen, and α_2-antiplasmin activities were assessed on chromogenic substrates. Samples for euglobulin lysis time were taken before and at the end of venous occlusion produced for 10 minutes by application of a cuff round the upper arm, which was inflated to a level midway between systolic and diastolic blood pressure. Euglobulin lysis time was determined in samples taken before venous occlusion and immediately before the depletion of the cuff.[11]

Statistical analysis. Results collected before and at the third and sixth months of the oral contraceptive treatment period were compared by a paired *t* test with use of an SAS program.[12] Moreover, the highest (+) or the lowest (−) extreme values of the ranges were selected for each parameter considering their hypothetic involvement in the thrombogenesis.

Results

Platelets. Platelet number, platelet aggregate ratio, and plasma β-thromboglobulin levels were not significantly modified during the treatment period.

No thrombocytosis occurred in any women, but low platelet aggregate ratio (increase in circulating aggregates) and high β-thromboglobulin plasma levels released from platelets were observed as shown by the extreme values (Table I).

The von Willebrand factor. The von Willebrand factor (vWF:Ag) but not ristocetin cofactor was significantly increased in treated women. The extreme values of the von Willebrand factor remained below 200% during the treatment period; extreme values of the ristocetin cofactor were already high before treatment.

Coagulation. Oral contraceptive treatment induced a significant increase in clottable fibrinogen, factor VII:C, and factor VIII:C levels (except for the latter at the third month). The highest extreme value of clottable fibrinogen was above usual upper reference values. The highest extreme value of factor VIII:C, which was observed at the sixth month, was the most impressive result of the study. In addition, only factor VIII:C was significantly increased from the third to the sixth month.

Antithrombin III activity was not significantly modified during the whole treatment period despite a significant decrease in its antigen concentration. However, at the sixth month, the lowest extreme value of antithrombin III activity was inferior to its corresponding baseline value.

Fibrinolysis. Both plasminogen antigen concentration and activity were significantly increased by oral contraceptives, mainly at the third month. The α_2-antiplasmin activity was significantly increased at the

Table I. Effects of oral contraceptives on platelets, von Willebrand factor, coagulation, and fibrinolysis

Test	Baseline			Treatment							
				+3 mo				+6 mo			
	n	Mean ± SD	E.V.*	n	Mean ± SD	E.V.	p	n	Mean ± SD	E.V.	p
Platelets											
No. ($10^3 \cdot l^{-1}$)	36	250 ± 47	393 (+)	33	256 ± 62	410 (+)	NS	31	257 ± 56	404 (+)	NS
PAR (index)	36	0.92 ± 0.03	0.83 (−)	33	0.92 ± 0.04	0.84 (−)	NS	31	0.92 ± 0.05	0.78 (−)	NS
Plasma thromboglobulin ($ng \cdot ml^{-1}$)	35	10 ± 9	39 (+)	31	10 ± 17	87 (+)	NS	29	14 ± 14	58 (+)	NS
von Willebrand factor											
vWF:Ag (%)	36	88 ± 29	148 (+)	33	113 ± 36	190 (+)	0.00002	31	103 ± 31	162 (+)	0.0184
RCof (%)	36	92 ± 38	250 (+)	33	110 ± 43	250 (+)	NS	31	107 ± 46	275 (+)	0.0067
Coagulation											
APTT (sec)	36	30 ± 4	23 (−)	33	28 ± 2	23 (−)	0.0025	31	27 ± 3	24 (−)	0.0003
Clottable fibrinogen (mg/dl)	36	2.5 ± 0.5	3.7 (+)	33	3 ± 0.8	5.3 (+)	0.0014	31	2.7 ± 0.5	4.1 (+)	0.0138
Factor VII:C (%)	36	81 ± 19	130 (+)	33	102 ± 27	170 (+)	0.0001	31	105 ± 27	150 (+)	0.0001
Factor VIII:C (%)	36	104 ± 29	200 (+)	33	114 ± 26	200 (+)	NS	31	130 ± 41†	280 (+)	0.0082
Antithrombin III antigen (mg/dl)	36	26 ± 3	21 (−)	33	24 ± 3	19 (−)	0.0001	31	24 ± 2	20 (−)	0.0148
Antithrombin III activity (inh. unit)	36	22 ± 3	17 (−)	33	22 ± 3	18 (−)	NS	31	22 ± 3	15 (−)	NS
Fibrinolysis											
Plasminogen antigen (mg/dl)	36	13 ± 3	7 (−)	33	17 ± 3	8 (−)	0.0001	31	16 ± 4	7 (−)	0.001
Plasminogen activity (%)	36	84 ± 13	51 (−)	33	111 ± 13	74 (−)	0.0001	31	107 ± 14	67 (−)	0.001
α-antiplasmin activity (%)	36	113 ± 14	139 (+)	33	124 ± 14	152 (+)	0.0011	31	121 ± 17	164 (+)	NS

PAR, Platelet aggregate ratio; *vWF:Ag*, von Willebrand cofactor and its related antigen; *RCof*, ristocetin cofactor; *APTT*, activated partial thromboplastin time.

*Extreme values were the highest (+) or lowest (−) individual extreme values (see statistical analysis).

†The difference between the effects observed at 3 and 6 months were significant only for factor VIII C ($p = 0.0318$).

Table II. Effects of oral contraceptive treatment on euglobulin lysis time; % of results < 60 minutes

	Baseline	Treatment		p (χ^2)
		3 mo	6 mo	
Before VO	17	22	28	N.S.
After VO	32	56	69	.048

VO, Venous occlusion.

third month and tended to remain elevated at the sixth month ($p = 0.0556$), with a more marked dispersion of the results.

The euglobulin lysis time (Table II) was significantly shortened only after venous occlusion.

Comment

Although most of the parameters controlled in this study were significantly modified during low estrogen oral contraceptive treatment, the alterations in mean and SD values were not very marked. These results are in accordance with those reported in other comparable studies.[13, 14] However, we believe that the extreme values observed among individual results were worthy of consideration, taking into account their possible involvement in the multifactorial pathogenesis of thrombotic events.

Thus the mean values of platelet aggregate ratio and plasma β-thromboglobulin were not significantly modified by oral contraceptives, but their extreme values strongly suggest that an in vivo platelet activation occurred in some healthy women during the treatment period.

The von Willebrand factor (vWF:Ag) was significantly increased during the treatment period and ristocetin cofactor was already increased before it. Although the meaning of elevation in von Willebrand factor is not clearly documented, it must be remembered that this factor is released from platelets and endothelial cells, thus playing a crucial role in platelet adhesion when the flow rate is such as to give high-wall shear stress.

The increase in factor VII:C, factor VIII:C, and fibrinogen was probably the result of the well-known effect of estrogen on protein synthesis by hepatocytes.

High levels of these factors do not imply an in vivo activation of coagulation, although epidemiologic studies have reported that thrombotic risk was linked to the level of fibrinogen and factor VII:C.

In our study, activated partial thromboplastin time, an ex vivo dynamic test of coagulation, was significantly shortened by oral contraceptive treatment, but its shortest time remained within the normal range of the usual laboratory references.

Antithrombin III activity, the main natural inhibitor of coagulation, was not reduced despite a slight but significant lowering of its antigenic plasma concentration.

As for coagulation factors, the increase in plasminogen and α_2-antiplasmin was probably induced by a nonspecific effect of estrogens on the hepatic synthesis of proteins.

A more interesting effect of oral contraceptive treatment is the shortening of euglobin lysis time that was measured at the end of local venous occlusion. An increase in the fibrinolytic potential may be considered a "protective" phenomenon resulting from oral contraceptives acting by either increasing the production of tissue plasminogen activator or depressing the production of its specific inhibitor. Whether this phenomenon is compromised in some subjects may be an important question to solve to detect women at risk of thrombotic events.

Finally, it must be emphasized that the results reported here were obtained in young healthy, nonsmoking women and were devoid of any clinical meaning. That does not imply that in other women with unknown lesions of the vessel wall or local disturbances of blood circulation, such as venous stasis or turbulences, individual marked alterations in hemostasis might not increase the thrombotic risk.

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Effects of long-term gestodene-containing oral contraceptive administration on hemostasis

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The purpose of this study was to evaluate the behavior of the hemostatic system during treatment with gestodene-containing oral contraceptives in monophasic (SHD 356, $n = 15$) and triphasic (SHD 415, $n = 15$) formulations. No changes in platelet (β-thromboglobulin, platelet aggregate ratio, and megathrombocyte) and routine clotting assays were observed. Factor VIIc/factor VIIag ratio and fibrinopeptide A values showed a significant ($p < 0.005$) increase after three cycles of both treatments. A slight, significant increase ($p < 0.01$) in antithrombin III activity was observed during triphasic treatment. Protein C was unchanged. Fibrinolytic activity and plasminogen levels were significantly increased ($p < 0.05$ and $p < 0.001$). After 6 and 9 months, the factor VIIc/factor VIIag ratio was still significantly enhanced, whereas fibrinopeptide A values significantly ($p < 0.05$) decreased, even if they were higher ($p < 0.05$) than basal values. The persistence of factor VII activation without enhanced thrombin formation after long-term use of oral contraceptives suggests that at that time the activity of antithrombotic mechanisms counteracts the prothrombotic tendency, thus helping to minimize unwanted side effects on hemostasis during long-term drug administration. (Am J Obstet Gynecol 1990;163:424-30.)

Key words: Gestodene, oral contraceptives, blood clotting, fibrinopeptide A, factor VII

Fibrin formation in vivo is modulated by two mechanisms, the blood clotting inhibitory system, which inactivates serine proteases and nonenzymatic cofactors, and the fibrinolytic system, which removes fibrin deposition. The relevant role of these physiologic regulatory mechanisms is supported by the increased occurrence of thromboembolic complications in inherited disorders with impairement of these antithrombotic activities.[1-3]

The use of oral contraceptives has been demonstrated to affect the hemostatic system, inducing an increase in procoagulant factor activities and a simultaneous decrease in the levels of the naturally occurring coagulation inhibitor, antithrombin III.[4, 5] These changes in the hemostatic system may at least partially account for the higher incidence of thrombotic disease associated with oral contraceptive treatment.[6]

In recent years the introduction of low-dose estrogen formulations has notably decreased the magnitude of changes in procoagulant and antithrombin III activity.[7-9] Moreover, with low-dose oral contraceptives, an increase in fibrinolytic activity has been found,[10] thus contributing to a reduced risk of thromboembolism.[11]

Previous reports by us[12, 13] on treatment with the recently developed combination of ethinyl estradiol and gestodene showed limited hemostatic changes. Gestodene is a novel progestogen of greater biologic activity than levonorgestrel, and it can be used in very low-dose oral contraceptives.[14]

The purpose of this longitudinal investigation was to assess blood clotting activation (fibrinopeptide A and factor VII) and the behavior of both physiologic inhibitors, antithrombin III and protein C, and the fibrinolytic system during long-term administration of ethinyl estradiol–gestodene in monophasic and triphasic formulations.

Material and methods

Subjects. Thirty healthy women, ages 17 to 45 years, were randomly allocated to receive nine treatment cycles of ethinyl estradiol–gestodene in monophasic (SHD 356, $n = 15$) or triphasic (SHD 415, $n = 15$) formulations.

The following inclusion criteria were used: no history of thrombotic disease or varices, normal dietary and life habits, not overweight, no pregnancy or oral contraceptive treatment for at least 9 months, and smoking habits of no more than 10 cigarettes per day. The two groups were comparable for age, weight, and life and smoking habits.

The monophasic formulation (SHD 356) contained 30 μg of ethinyl estradiol and 75 μg of gestodene. The triphasic formulation (SHD 415) contained six tablets of 30 μg of ethinyl estradiol + 50 μg of gestodene, five

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Table I. Platelet count ($\times 10^3/mm^3$), megathrombocyte percentage, platelet aggregate ratio, and β-thromboglobulin concentration before and during monophasic (SHD 356) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
Platelet count					
Mean	195.28	198.63	194.72	200.75	205.00
SD	±47.91	±45.23	±37.94	±39.61	±41.49
*p**		NS	NS	NS	NS
Megathrombocyte					
Mean	20.96	18.95	21.95	20.01	21.74
SD	±4.99	±3.99	±3	±2.49	±2.80
p		NS	NS	NS	NS
Par					
Mean	0.98	0.99	0.97	0.98	0.97
SD	±0.07	±0.08	±0.07	±0.08	±0.08
p		NS	NS	NS	NS
β-TG (ng/ml)					
Mean	21.01	21.9	19.9	23.05	22.42
SD	±7.14	±7.9	±8.9	±8.01	±9.1
p		NS	NS	NS	NS

PAR, Platelet aggregate ratio; *β-TG*, β-thromboglobulin.
**p* Values after cycles 1, 3, 6, and 9 compared with pretreatment values.

tablets of 40 μg of ethinyl estradiol + 70 μg of gestodene, and 10 tablets of 30 μg of ethinyl estradiol + 100 μg of gestodene.

Blood samples were taken before treatment was started and between days 25 and 28 of treatment during the first, third, sixth, and ninth cycles from subjects fasting overnight.

Subjects were free from any other drug in the 2 weeks preceding blood sampling.

Methods. Platelet and megathrombocyte counts were performed in whole blood by the platelet analyzer 810 (Baker Instruments, Allentown, Pa.). Platelet aggregate ratio was carried out according to Wu and Hoak.[15] β-Thromboglobulin concentration was measured in platelet-poor plasma by radioimmunoassay (Amersham International, United Kingdom) according to Ludlam and Cash.[16] Fibrinopeptide A was measured in platelet-poor plasma by radioimmunoassay with a kit purchased from Mallinckrodt Inc. (St. Louis, Mo.), according to Hofmann and Straub.[17] Factor VII clotting activity was performed in plasma by one-stage clotting assay with human brain thromboplastin.[18] Factor VII antigen was measured by immunoenzymatic assay (enzyme-linked immunoassay, Stago, Asnieres sur Seine, France).[19] Antithrombin III activity was assayed by the amidolytic method[20] by means of automated equipment (Allied Instrumentation Laboratory, Milan, Italy). Protein C was measured by coagulant assay (Behringwerke, Marburg, Federal Republic of Germany).[21] Spontaneous plasma fibrinolytic activity was assayed by euglobulin clot lysis time and was expressed as fibrinolytic units, which were obtained by dividing 1300 by lysis time (minutes).[22] Plasminogen assay was performed by the amidolytic method[23] with automated equipment (Allied Instrumentation Laboratory). Routine blood clotting tests (fibrinogen, activated partial thromboplastin time, and prothrombin time) were performed.

Statistical analysis. Results are expressed as mean ± standard deviation (SD).

Statistical analysis was carried out with the Student *t* test for paired data.

Results

During both treatments, no significant differences in platelet and megathrombocyte counts, circulating platelet aggregates, and β-thromboglobulin plasma levels (Table I and Table II) were observed.

Fibrinopeptide A plasma levels increased throughout the study after only one cycle of both treatments (Table III). The maximum increase was observed after the first cycle during monophasic treatment ($p < 0.001$) and after the third cycle during triphasic treatment ($p < 0.005$).

At subsequent observations, fibrinopeptide A values showed a tendency to decrease; after nine cycles of monophasic treamtent, fibrinopeptide A levels were significantly ($p < 0.05$) lower compared with first cycle values. After six and nine cycles of triphasic treatment, fibrinopeptide A levels significantly ($p < 0.05$) decreased compared with third cycle values, even if they were still significantly higher than baseline values ($p < 0.05$).

Factor VII clotting activity and factor VII antigen rose during the treatments, but the increase in factor VII clotting activity was greater than that of factor VII

Table II. Platelet count ($\times 10^3/mm^3$), megathrombocyte percentage, platelet aggregate ratio, and β-thromboglobulin concentration before and during triphasic (SHD 415) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
Platelet count					
Mean	197.92	201.15	203.12	198.97	195.62
SD	±43.68	±36.28	±40.32	±41.29	±44.91
*p**		NS	NS	NS	NS
Megathrombocyte					
Mean	21.95	20.97	19.9	22.1	22.4
SD	±3	±4.99	±5.9	±4.09	±4.65
p		NS	NS	NS	NS
PAR					
Mean	0.97	0.98	1.02	0.99	0.98
SD	±0.08	±0.09	±0.09	±0.08	±0.07
p		NS	NS	NS	NS
β-TG (ng/ml)					
Mean	22.97	24.9	24	23.97	21.73
SD	±6.4	±9.19	±8.01	±4.71	±7.3
p		NS	NS	NS	NS

PAR, Platelet aggregate ratio; *β-TG,* β-thromboglobulin.
**p* Values after cycles 1, 3, 6, and 9 compared with pretreatment values.

Table III. Fibrinopeptide A (ng/ml) plasma levels before and during monophasic (SHD 356) and triphasic (SHD 415) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
SHD 356					
Mean	1.15	2.87	2.58	2.02	2.05
SD	±0.41	±1.15	±1.42	±1.22	±1.4
p		<0.001	<0.005	<0.05	<0.05
*p**			NS	NS	<0.05
SHD 415					
Mean	1.28	2.48	2.71	2.07	2.2
SD	±0.4	±1.4	±1.6	±1.2	±1.7
p		<0.005	<0.005	<0.05	<0.05
p†		NS		<0.05	<0.05

p Levels after cycles 1, 3, 6, and 9 compared with pretreatment levels.
**p* Levels after cycles 3, 6, and 9 compared with first cycle levels.
†*p* Levels after cycles 1, 6, and 9 compared with third cycle levels.

Table IV. Ratio factor VIIc/VIIag before and during monophasic (SHD 356) and triphasic (SHD 415) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
SHD 356					
Mean	1.20	2.03	2.28	2.37	2.34
SD	±0.22	±0.63	±0.71	±0.8	±0.7
p		<0.01	<0.005	<0.005	<0.005
SHD 415					
Mean	1.22	—	2.37	2.68	2.65*
SD	±0.30	—	±1.10	±1.19	±1.2
p			<0.01	<0.005	<0.01

p Values after cycles 1, 3, 6, and 9 compared with pretreatment values.
**n* = 8.

Table V. Antithrombin III activity (percentage) before and during monophasic (SHD 356) and triphasic (SHD 415) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
SHD 356					
Mean	100.05	101.01	102.9	102.05	101.8
SD	±8	±9.18	±8.29	±7.91	±8.5
p		NS	NS	NS	NS
SHD 415					
Mean	98.03	99.03	106.03	106.79	100.2
SD	±7.7	±8.21	±8.7	±11.22	±9.3
p		NS	<0.01	<0.01	NS

p Values after cycles 1, 3, 6, and 9 compared with pretreatment values.

Table VI. Protein C activity (percentage) before and during monophasic (SHD 356) and triphasic (SHD 415) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
SHD 356					
Mean	97.48	101.83	99.67	98.39	102.13
SD	±11.22	±13.21	±10.9	±11.61	±12.14
p		NS	NS	NS	NS
SHD 415					
Mean	102.37	101.92	105.65	106.64	104.4
SD	±12.8	±9.45	±11.95	±12.23	±10.96
p		NS	NS	NS	NS

p Values after cycles 1, 3, 6, and 9 compared with pretreatment values.

antigen, so that the factor VII clotting activity/factor VII antigen ratio was significantly enhanced at all cycles investigated (Table IV).

Antithrombin III activity showed no significant changes during monophasic treatment (Table V). During triphasic treatment, antithrombin III activity was unmodified after the first cycle, whereas a slight but significant increase was observed at cycles 3 and 6. After nine cycles, antithrombin III activity was not statistically different from baseline values (Table V).

Protein C, assayed as functional activity, was unaltered throughout the study during both treatments (Table VI).

Fibrinolytic activity, which was evaluated as euglobulin clot lysis time, and plasminogen concentration significantly increased after only the first cycle of both pill administrations and remained elevated throughout the treatment period (Tables VII and VIII).

No changes in fibrinogen, activated partial thromboplastin time, and prothrombin time were observed (data not shown).

Comment

Our findings indicate that during the administration of both ethinyl estradiol–gestodene formulations, some prothrombotic changes take place. Significant blood clotting activation occurs during the first months of both treatments as indicated by increased levels of fibrinopeptide A, which provides reliable evidence of increased thrombin generation in vivo. In fact fibrinopeptide A represents the first fragment split from fibrinogen by trace amounts of thrombin.[24] The blood clotting activation that was observed in this study seems small because no changes in platelet functions were found, thus indicating that thrombin generation did not reach the amount (0.01 IU/ml) needed to trigger platelet activation.[25] The rise in fibrinopeptide A levels was similar in magnitude and time course to that found during the administration of low-dose treatment with levonorgestrel[8] and cyproterone acetate,[9] and it was notably smaller than that observed with the 50 μg estrogen formulation.[26]

In this study we have investigated the factor VII clotting activity/factor VII antigen ratio for the assessment of a hypercoagulable state. In fact, the study of factor VII provides notable insight into its particular characteristics in the regulation and initiation of coagulation.[27, 28] During the two treatments, both factor VII clotting activity and factor VII antigen were increased, but there was a greater rise in factor VII clotting activity compared with factor VII antigen. The enhancement of the factor VII clotting time/factor VII antigen ratio

Table VII. Fibrinolytic activity (fibrinolytic units) before and during monophasic (SHD 356) and triphasic (SHD 415) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
SHD 356					
Mean	8.1	11.6	11.9	12.1	11.3
SD	±3.4	±5.2	±6	±5.6	±5.7
p		<0.05	<0.05	<0.05	<0.05
SHD 415					
Mean	7.8	12	13.2	13.4	12.9
SD	±4.1	±4.8	±5.4	±5.1	±6.2
p		<0.05	<0.05	<0.01	<0.05

p Values after cycles 1, 3, 6, and 9 compared with pretreatment values.

Table VIII. Plasminogen concentration (percentage) before and during monophasic (SHD 356) and triphasic (SHD 415) treatment

		Cycle			
	Before	*1st*	*3rd*	*6th*	*9th*
SHD 356					
Mean	94.2	125.5	131.7	137.2	132.3
SD	±7.3	±9.2	±10.9	±12.4	±11.7
p		<0.001	<0.001	<0.001	<0.001
*p**			NS	<0.05	NS
SHD 415					
Mean	101.1	124.2	147.2	135.6	130.5
SD	±8.2	±10.1	±11	±10.2	±11.2
p		<0.001	<0.001	<0.001	<0.001
*p**			<0.001	<0.01	NS

p Values after cycles 1, 3, 6, and 9 compared with pretreatment values.
**p* Values after cycles 3, 6, and 9 compared with first cycle values.

suggests that an increase in the functional activity of factor VII rather than only an increase in its concentration occurs.

The enhancement of factor VII clotting activity during pill administration could be attributed to the activation of factor VII by factor XII, which has been found to be increased after oral contraceptive administration.[29, 30] Oral contraceptives are known to modify the lipoprotein pattern, inducing an increase in very low–density lipoprotein and chylomicron levels.[31] The negative charges of these lipoproteins have been demonstrated to interact with factor XII, facilitating its conversion into its active conformation,[32, 33] which, in turn, can promote factor VII activation.

During the first three cycles of therapy, the increase in the factor VII clotting activity/factor VII antigen ratio was associated with coagulation activation, as demonstrated by a rise in fibrinopeptide A levels. Subsequently, even if the enhancement of factor VII clotting activity/factor VII antigen subsided, thrombin production showed a significant decrease, thus indicating that no further increase in blood clotting activation occurs, even if the prothrombotic stimulus persists.

In our study we observed a significant increase in fibrinolytic activity and plasminogen levels. The increase in plasminogen activity could be caused by decreased levels of histidine-rich-glycoprotein during low-dose oral contraceptive treatment.[34] In fact, histidine-rich glycoprotein binds to the high-affinity lysine-binding sites of plasminogen and interferes with the binding of plasminogen to fibrin.[35]

In conclusion, the physiologic antithrombotic mechanisms, antithrombin III, protein C, and the fibrinolytic system, counteract the coagulant tendency observed during low-dose ethinyl estradiol–gestodene treatment, thus helping to minimize unwanted side effects on hemostasis during long-term drug administration.

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Comparative studies of 30 μg ethinyl estradiol combined with gestodene and desogestrel on blood coagulation, fibrinolysis, and platelets

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An association between an increase in the incidence of thromboembolic disease and the use of combined oral contraceptives has been shown by several epidemiologic studies. Evidence of the vascular complications of oral contraceptives suggests that venous thromboembolism correlates with estrogen dosage and arterial complications with both estrogen and progestogen components. In 60 healthy, randomly allocated women, the effects of ethinyl estradiol, 30 μg, combined with gestodene, 75 μg, and desogestrel, 150 μg, on blood coagulation, fibrinolysis, and platelet function were compared. Subjects were studied before oral contraceptive use, at 12, 24, 36, and 48 weeks of treatment, and at 6 and 12 weeks after treatment. Both oral contraceptives affected the hemostatic system, but our results indicate that the ethinyl estradiol/gestodene combination causes changes in the hemostatic system similar to those in the ethinyl estradiol/desogestrel combination. Factors VII and X activity were slightly higher with the ethinyl estradiol/desogestrel combination than with the ethinyl estradiol/gestodene combination, possibly reflecting a greater estrogenic effect. (AM J OBSTET GYNECOL 1990;163:430-7.)

Key words: Oral contraceptives, coagulation, fibrinolysis, dosage of estrogen, type of progestogen

Since the introduction of oral contraceptives in the early 1960s, several epidemiologic studies have reported an association between their use and an increased risk of vascular disease. The main vascular complications are venous thromboembolic disease, myocardial infarction, and hemorrhagic and thrombotic strokes.[1-5] This risk appears to have decreased in parallel with a reduction in the estrogen content.[6-8] The progestogen component of the pill modifies the estrogen effects on blood coagulation[9,10] and may contribute to the increased risk of stroke and ischemic heart disease.[10-12] New formulations of oral contraceptives have recently been introduced containing low doses of estrogen in combination with new progestogens. This study is designed to examine the effects of two new combined oral contraceptives on blood coagulation, fibrinolysis, and platelet function. These pills contain 30 μg of ethinyl estradiol, in combination with gestodene or desogestrel, in monophasic formulations.

Material and methods

Subjects. Sixty healthy women who were between the ages of 18 and 34 years with no contraindications to estrogen/progestogen therapy took part in the study. Women who smoked 15 cigarettes or more per day were excluded. Subjects were randomly allocated to two groups: (1) group 1: 30 women taking Femodene, containing 30 μg of ethinyl estradiol + 75 μg of gestodene, 21 tablets per cycle, and (2) group 2: 30 women taking Marvelon, containing 30 μg of ethinyl estradiol + 150 μg of desogestrel, 21 tablets per cycle.

Method and timing of blood collection. Venous blood specimens were taken between 10:00 AM and noon each morning in the control cycle and thereafter at 12, 24, 36, and 48 weeks of treatment and at 6 and 12 weeks after hormone treatment. In the pretreatment cycle, blood samples were taken between days 21 and 24 of the cycle. In the treatment cycles blood samples were taken between days 15 and 21 of tablet administration.

Laboratory methodology. Prothrombin time,[13] activated thromboplastin time,[14] factor VII activity,[15] and fibrinogen[16] were assayed by standard laboratory techniques. Specific chromogenic substrates were used to assay plasminogen,[17] antithrombin III,[18] factor X,[19], anti-Xa,[20] and antiplasmin.[21] Plasminogen activator was measured by means of the euglobulin precipitate and the fibrin plate technique.[22] The Chandler tube method[23] was used to measure thrombin-induced platelet aggregation, and platelets were counted with a Thrombocounter-C.[24] Prothrombin clotting time, factor VII, activated thromboplastin time, platelet aggregation, platelet count, and fibrin plate assay were car-

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6/0/17865

ried out within 1 hour of venipuncture. Factor X, anti-Xa, antiplasmin, plasminogen, antithrombin III, and fibrinogen were assayed on fresh-frozen plasma stored at −20° C.

Statistical analysis. The null hypothesis was that both oral contraceptives were equal with respect to the hemostatic parameters that were measured. The alternative hypothesis was that with a sample size of 30 women in each treatment group, a type I error of $\alpha = 0.05$, and a test power of $1 - \beta = 0.90$, a t test would detect a difference of $\Delta = 0.8^* \sigma$. The maximal increase or minimal decrease in the treatment phase was analyzed with an analysis of covariance (covariate = prevalue of the appropriate variable, dependent variable = maximal increase or minimal decrease at $\alpha = 0.05$). Similarly, the values of 12 weeks after treatment were analyzed with an analysis of covariance with the prevalues as covariate at $\alpha = 0.05$. Descriptive statistics (average, minimum, maximum, percentage averages, and box plots) (Fig. 1) were computed for all variables. Student t tests were used to determine the level of significance of the observed changes within the groups.

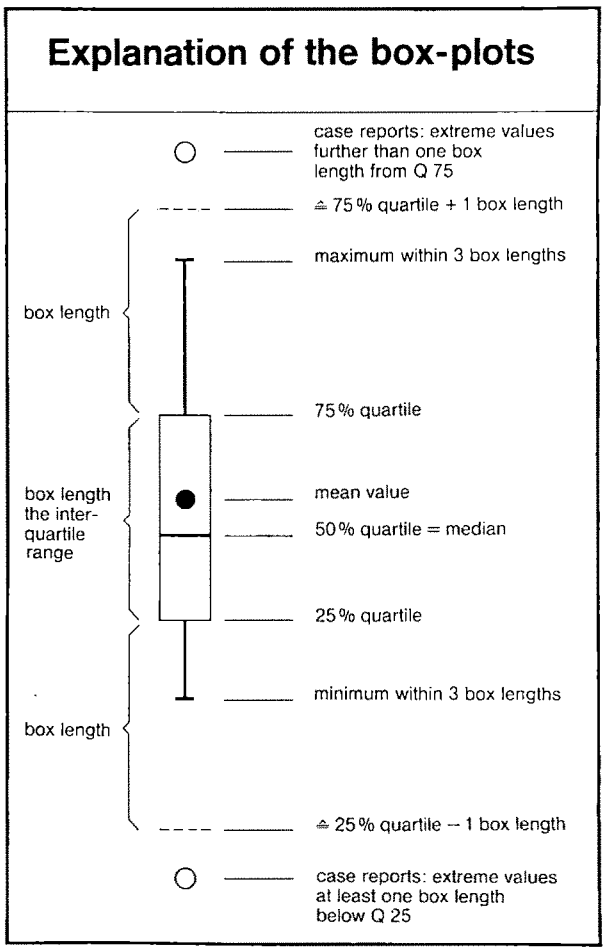


Fig. 1. Description of box plots.

Results

Coagulation system

Prothrombin time. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase has a positive slope $\beta = 0.05$; Fig. 2 shows a stable progression of the average time curve.

Activated partial thromboplastin time. There were no observable differences between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase over the treatment phase has a negative slope $\beta = -0.17$; Fig. 3 shows a slight decrease in the average time curve.

Factor VII. Factor VII clotting time was decreased at 12, 24, 36, and 48 weeks in women taking either the desogestrel or the gestodene combination, which indicated an increase in factor VII activity ($p < 0.001$); the decrease was slightly greater in those women taking the desogestrel combination. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase over the treatment phase has a positive slope $\beta = 0.34$ ($p < 0.05$), but Fig. 4 shows a decrease in the average time curve.

Factor X. Factor X was increased at 12, 24, 36, and 48 weeks of treatment when compared with pretreatment levels in both groups ($p < 0.001$); the increase was slightly greater in the desogestrel group. Factor X activity 6 weeks after treatment was decreased from that at 48 weeks while receiving treatment. There was no observable difference between treatments in the treatment phase ($p > 0.05$), but 12 weeks after treatment there was a difference between the two treatment groups ($p < 0.05$). The level of factor X for the desogestrel group was higher than that for the gestodene group. The maximal increase over the treatment phase has a positive slope $\beta = 0.14$; Fig. 5 shows a slight increase in the average time curve.

Antithrombin III. Antithrombin III levels were decreased at 36 weeks in women taking either combination ($p < 0.01$). At 6 weeks after treatment, the antithrombin III levels of both groups had returned to within the normal range. There were no observable differences in antithrombin III levels between treatments in the treatment and posttreatment phases ($p > 0.05$). The minimal decrease over the treatment phase has a positive slope $\beta = 0.38$; Fig. 6 shows a stable progression of the average time curve.

Anti-Xa. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The minimum decrease over the treatment phase has a negative slope $\beta = -0.11$; Fig. 7 shows a slight decrease in the average time curve.

Fibrinolytic system

Plasminogen. Plasminogen levels at 12, 24, 36, and 48

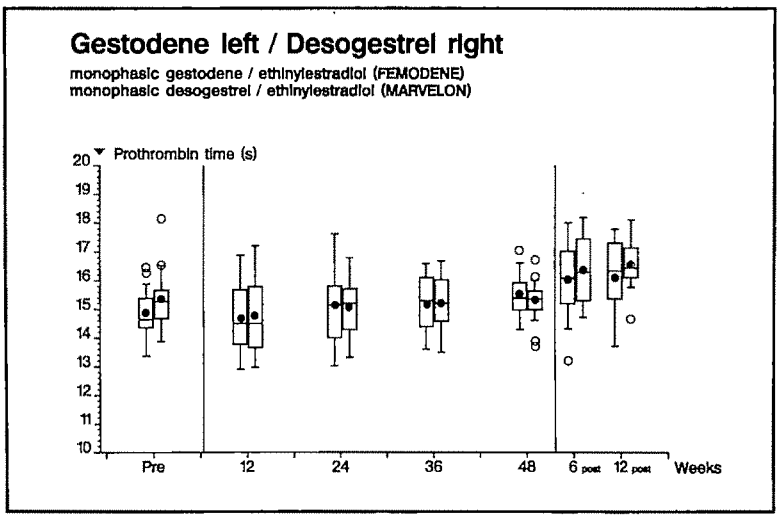


Fig. 2. Effects of gestodene and desogestrel on prothrombin time.

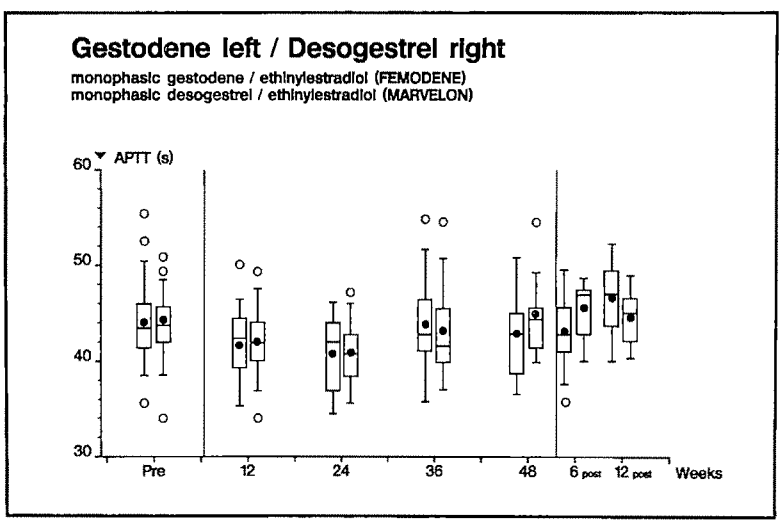


Fig. 3. Effects of gestodene and desogestrel on activated partial thromboplastin time.

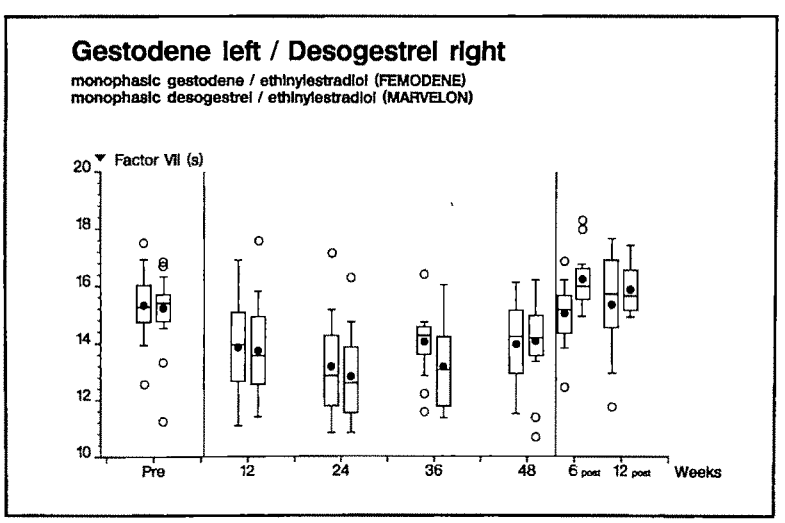


Fig. 4. Effects of gestodene and desogestrel on factor VII.

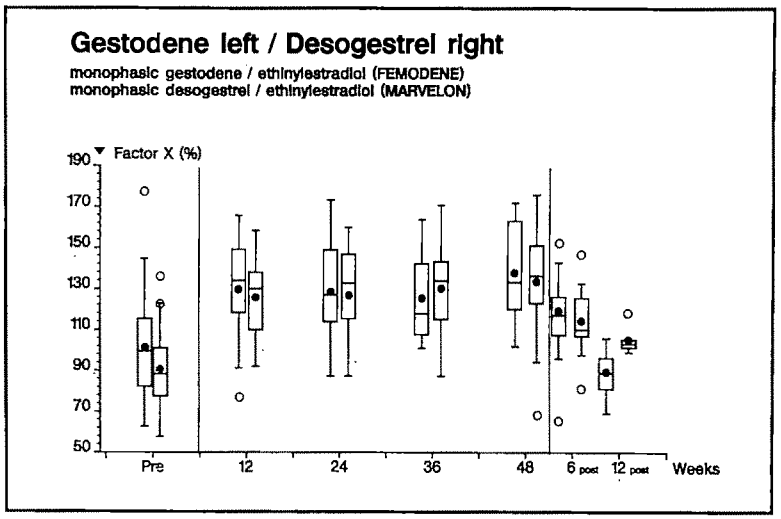


Fig. 5. Effects of gestodene and desogestrel on factor X.

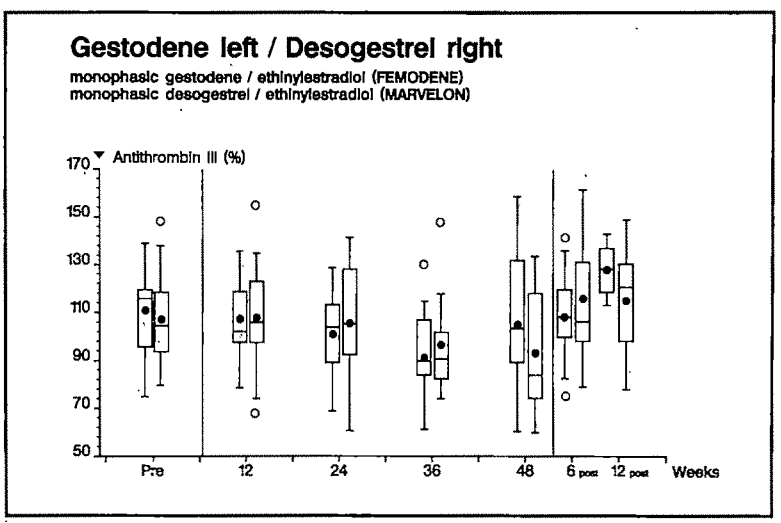


Fig. 6. Effects of gestodene and desogestrel on antithrombin III.

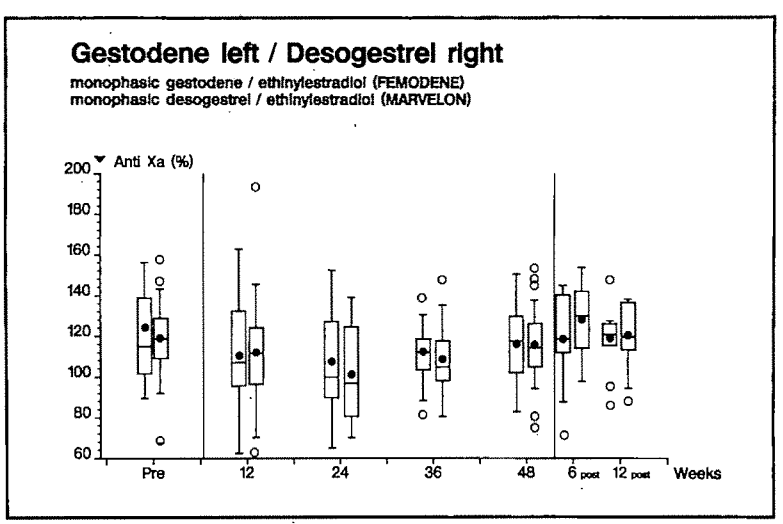


Fig. 7. Effects of gestodene and desogestrel on anti-Xa.

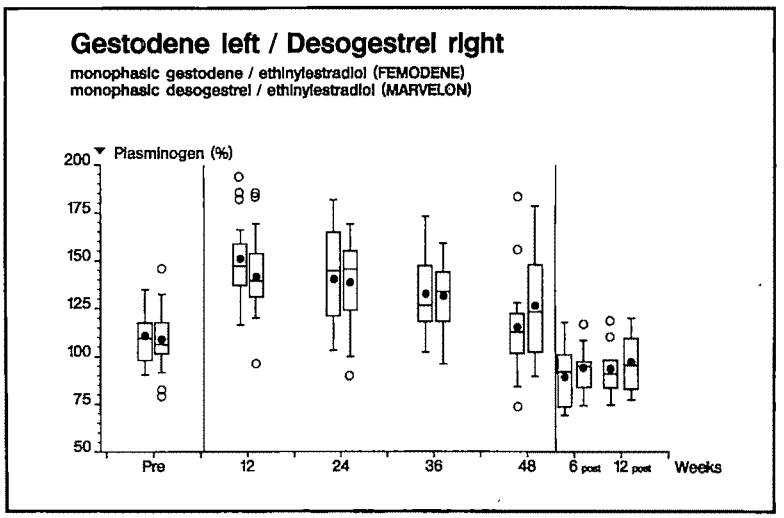


Fig. 8. Effects of gestodene and desogestrel on plasminogen.

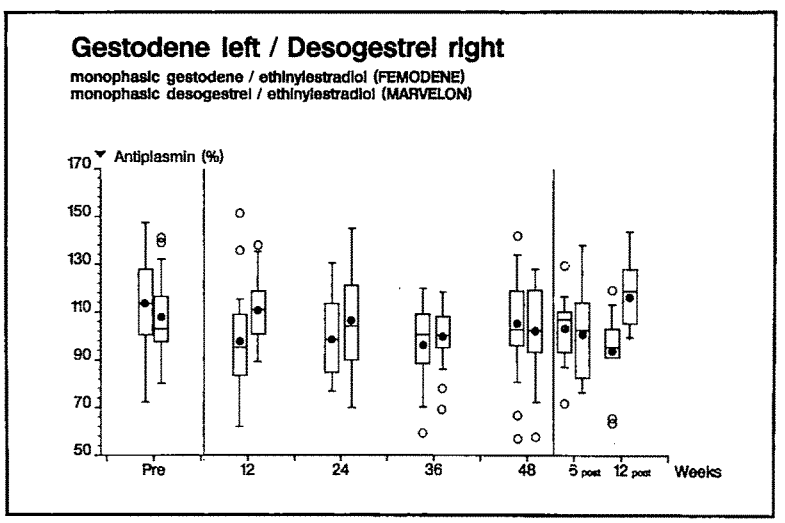


Fig. 9. Effects of gestodene and desogestrel on antiplasmin.

weeks were increased by both pills ($p < 0.001$). There was a difference between treatments in the treatment phase ($p < 0.05$), and there was no difference between treatments 12 weeks after treatment ($p > 0.05$). The plasminogen level was higher in the gestodene group than in the desogestrel group. The maximal increase over the treatment phase has a positive slope $\beta = 0.08$; Fig. 8 shows a slight increase in the average time curve.

Antiplasmin. There was no observable difference between treatments in the treatment phase ($p > 0.05$), but there was a difference between the two treatment groups 12 weeks after treatment ($p < 0.05$). The antiplasmin level was higher in the desogestrel group than in the gestodene group. The maximal increase over the treatment phase has a negative slope $\beta = -0.33$; Fig. 9 shows a slight decrease in the average time curve.

Fibrinogen. Fibrinogen levels increased with both pills ($p < 0.01$) and returned to pretreatment levels after treatment. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase over the treatment phase has a positive slope $\beta = 0.24$; Fig. 10 shows a slight increase in the average time curve.

Fibrinolytic activity. Fibrinolytic activity increased from 12 weeks on treatment in both groups ($p < 0.001$). During treatment increased fibrinolytic activity was sustained and rapidly returned to pretreatment levels 6 weeks after the pill was stopped. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase over the treatment phase has a positive slope

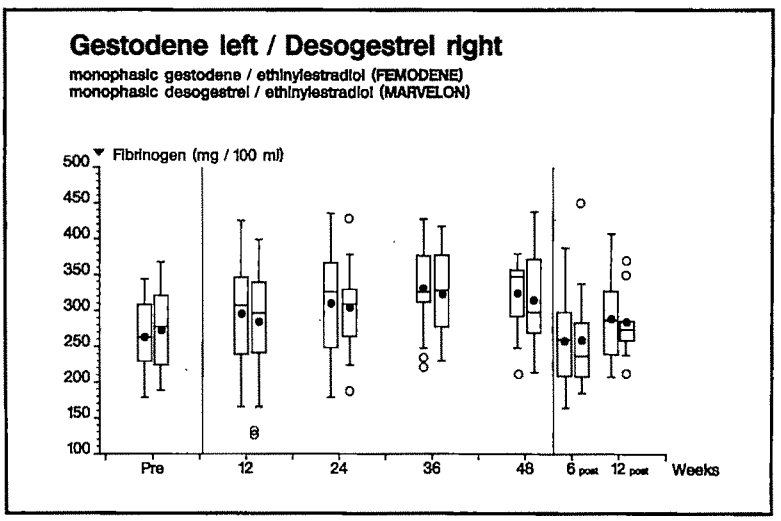


Fig. 10. Effects of gestodene and desogestrel on fibrinogen.

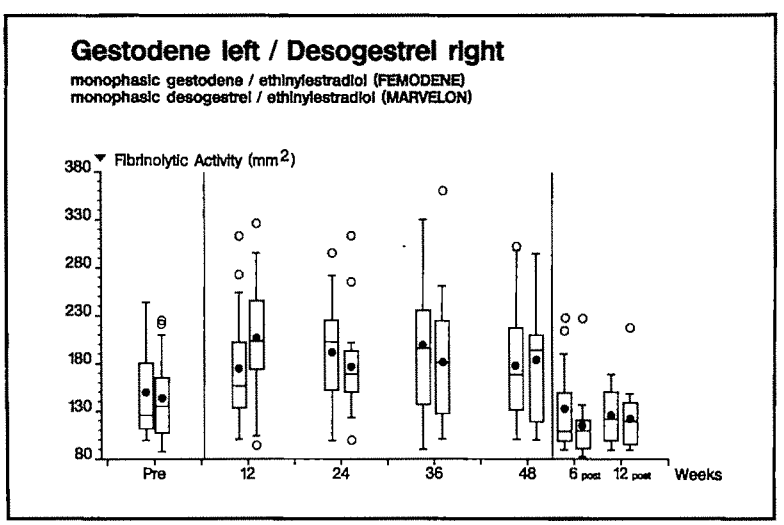


Fig. 11. Effects of gestodene and desogestrel on fibrinolytic activity.

$\beta = 0.22$; Fig. 11 shows a slight increase in the average time curve.

Platelets

Platelets aggregation. Platelet aggregation was decreased in both groups and the decrease was greater in the desogestrel group ($p < 0.001$) than in the gestodene group ($p < 0.01$). There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The minimal decrease over the treatment phase has a slope $\beta = 0.20$, but Fig. 12 shows a slight decrease in the average time curve.

Platelet count. There was no observable difference between treatments in the treatment and posttreatment phases ($p > 0.05$). The maximal increase over the treatment phase has a slope $\beta = 0.00$; Fig. 13 shows a stable progression in the average time curve.

Comment

The new low-dose estrogen/progestogen oral contraceptives induce major changes in the coagulation and fibrinolytic systems and in platelet function. The prothrombin time and activated partial thromboplastin time, which measure the overall activity of the extrinsic and intrinsic coagulation pathways, respectively, showed no significant changes with both oral contraceptive formulations. This indicates that the overall effects of the new pills are less than what occurs with the 50 μg pills that induce significant changes in these tests.[9] Likewise, changes in the coagulation system with respect to factor X, antithrombin III, and platelet aggregation are not as marked with the new low-dose monophasic oral contraceptives as with those previously studied that contained 50 μg of estrogen.[10] Both estro-

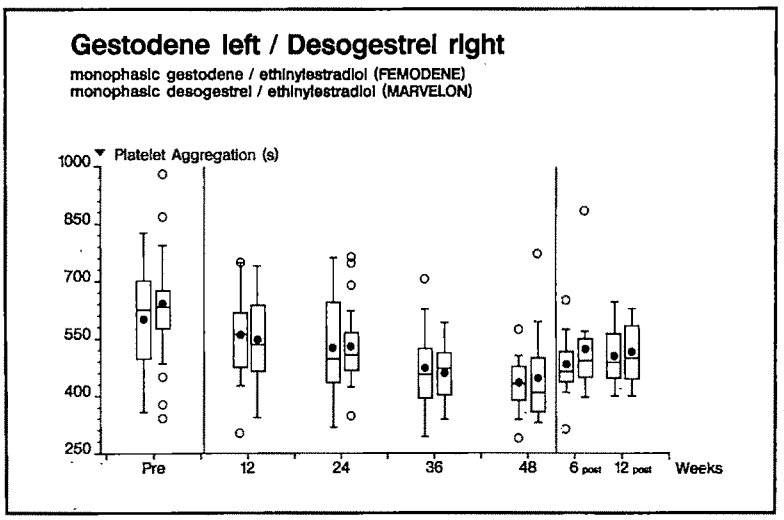


Fig. 12. Effects of gestodene and desogestrel on platelet aggregation.

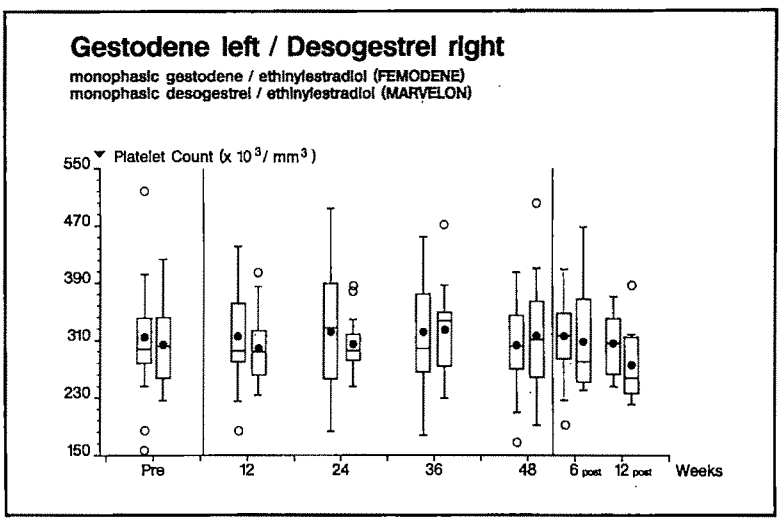


Fig. 13. Effects of gestodene and desogestrel on platelet count.

gen/progestogen pills increased significantly the activity or factors VII and X, and the greater increase with the desogestrel pill suggests this combination has a greater estrogenic effect. Plasminogen and fibrinolytic activity were markedly increased by both hormonal preparations, and this enhancement of fibrinolysis is likely to counteract the increase in fibrinogen and coagulation activity that protects the dynamic balance between coagulation and fibrinolysis. Platelet aggregation was decreased by both pills and more so by the desogestrel combination. This would seem to be an undesirable effect.

The low-dose oral contraceptives with the new progestogens studied induce marked changes in the hemostatic system, in particular, enhanced activity of factors VII and X and acceleration of platelet aggregation. These changes in the physiology of hemostasis suggest that these new pills will also carry a thrombogenic hazard in susceptible women. The effects on hemostasis arise from the overall estrogenic activity, which is determined by the progestogen used in combination with the estrogen. More research is required to find whether effective combinations can be obtained that will induce fewer changes in the hemostatic system and other physiologic processes. Meantime, it would be unwise for any claims to be made that oral contraceptives with the new progestogens, gestodene and desogestrel, will be free of vascular complications.

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Enhanced generation and resolution of fibrin in women above the age of 30 years using oral contraceptives low in estrogen

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Epidemiologic studies have suggested a relationship between the use of oral contraceptives and mortality from cardiovascular diseases in older women. Therefore we studied generation and resolution of fibrin in 28 healthy women above age 30 years, using oral contraceptives containing 30 to 50 μg of ethinyl estradiol. Thirty healthy nonusers served as control subjects. The oral contraceptive group had increased plasma concentration of thrombin–antithrombin III complexes ($p < 0.01$), which indicated an enhanced generation of thrombin, increased plasma activity of tissue-type plasminogen activator ($p < 0.01$), decreased plasma activity of plasminogen activator inhibition ($p < 0.01$), and increased plasma concentration of fibrin degradation products ($p < 0.04$). Interestingly, the ratio of thrombin–antithrombin III complexes/fibrin degradation products did not deviate significantly between groups. Twelve of the 28 women using oral contraceptives were light smokers, that is, less than 15 cigarettes per day. There were no differences in the determined variables between smokers and nonsmokers. Our study suggests that healthy women older than 30 years who use oral contraceptives containing 30 to 50 μg of ethinyl estradiol have an enhanced generation and resolution of fibrin, while the hemostatic balance is unaltered. These findings are unaffected by moderate cigarette smoking. (Am J Obstet Gynecol 1990;163:438-42.)

Key words: Oral contraceptives, tissue-type plasminogen activator, coagulation, fibrin degradation products

The results of epidemiologic studies have indicated that women taking oral contraceptives have an increased risk of cardiovascular disease.[1-4] A further stratification of the epidemiologic results suggests that the risk of thrombosis is particularly linked to older oral contraceptive users.

One of the most important concepts regarding the risk of thrombosis in users of oral contraceptives concerns a defective hemostasis.[5,6] An enhanced formation of fibrin caused by an active coagulation or a defective fibrinolysis might result in a state of clinical thrombosis.[5] Thus it is well known that the use of oral contraceptives should be avoided in women with congenital errors in the inhibition of coagulation, such as antithrombin III, protein C, or protein S deficiencies.[7-9] Less clinical information has been obtained from studies on fibrinolysis.

We have studied the activation of coagulation and fibrinolysis in healthy women with an apparently increased risk of thrombosis, that is, women older than 30 years, who use oral contraceptives low in estrogen.

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6/0/19258

Table I. Clinical characteristics in 28 healthy women receiving oral contraceptives (oral contraceptive group) low in estrogen (30 to 50 μg of ethinyl estradiol) and in 30 healthy women (control group); medians and ranges are shown

	OC group	*Control group*
Age (yr)	42 (31-48)	41 (31-49)
Weight (kg)	62 (52-85)	66 (53-96)
Systolic BP (mm Hg)	130 (115-150)	130 (40-170)
Diastolic BP (mm Hg)	80 (75-95)	85 (80-100)
Smokers *(n)*	12	14

OC, Oral contraceptive; *BP*, blood pressure.

By means of new specific assays, we could obtain information of the in vivo generation of thrombin and resolution of fibrin. In addition, we studied in more details the activation and inhibition of tissue-type plasminogen activator.

Material and methods

Subjects. Twenty-eight healthy women above the age of 30 years using low-dose oral contraceptives (30 to 50 μg of ethinyl estradiol) for at least 3 months were involved in the study (oral contraceptive group). Serving as controls were 30 healthy women above the age of 30 years, who had not taken any drugs (control group). The two groups of women were comparable

Table II. Hemostatic variables (medians and 25 to 75 interpercentile ranges) in 28 healthy oral contraceptive users stratified as light smokers (<15 cigarettes/day) and nonsmokers

	Smokers (n = 12)	*Nonsmokers (n = 16)*
TAT complexes (μg/L)	3.3 (3.1-4.2)	3.5 (2.6-4.9)
t-PA activity (mm^2)	34 (26-38)	34 (17-45)
PAI activity (IU/ml)	4.0 (2.7-6.1)	5.4 (4.9-6.7)
FbDP (μg/ml)	0.27 (0.17-0.33)	0.22 (0.17-0.24)
TAT complexes/FbDP ($\times 10^{-3}$)	17.1 (9.6-25.8)	16.2 (13.0-21.2)

TAT, Thrombin–antithrombin III; *t-PA,* tissue-type plasminogen activator; *PAI,* plasminogen activator inhibition; *FbDP,* fibrin degradation products.

with respect to age, weight, systolic and diastolic blood pressures, and the number of light smokers, that is, less than 15 cigarettes per day (Table I).

Blood collection and preparation. Blood samples were collected in the morning between 8:00 and 9:00 AM between days 11 and 14 in the menstrual cycle from fasting individuals. Samples were anticoagulated with trisodium citrate (4.5 ml blood; 0.5 ml 0.13 mol/L trisodium citrate) and tripotassium ethylene diamine tetraacetate (30 ml blood; 0.06 ml 0.17 mol/L EDTA). The blood sampling, the preparation of plasma samples, and the handling of the specimens followed standardized procedures.[10]

Assays. As a measure of in situ generation of thrombin, we determined thrombin–antithrombin III complexes by means of a commercially available enzyme-linked immunoassay method (Behringwerke, Marburg, West Germany) and expressed the results in μg/L according to a calibrator solution delivered by the manufacturer.[11] The plasma activities of the tissue-type plasminogen activator were determined on fibrin plates by the use of a standardized technique[12] and the results expressed as mm^2. The plasma activities of the plasminogen activator inhibition were determined by addition to the plasma samples of human two-chain melanoma tissue-type plasminogen activator (Organon Teknika, Turnhout, Belgium) as previously described[13] and the results expressed as IU/ml calibrated against the international standard preparation (Lot No. 83/517[14]). The plasma concentrations of fibrin degradation products were determined by a commercially available enzyme-linked immunoassay method (Organon Teknika) and the results expressed as μg/ml according to a calibrator delivered from the manufacturer. It should be noted that the antibodies used in the fibrin degradation product assay did not cross-react with fibrinogen degradation products.[15]

Statistical methods. Significant differences between the two groups of women were evaluated by means of the Mann Whitney test and Fisher's exact test. The individual data, medians, and quartiles are presented in the illustrations.

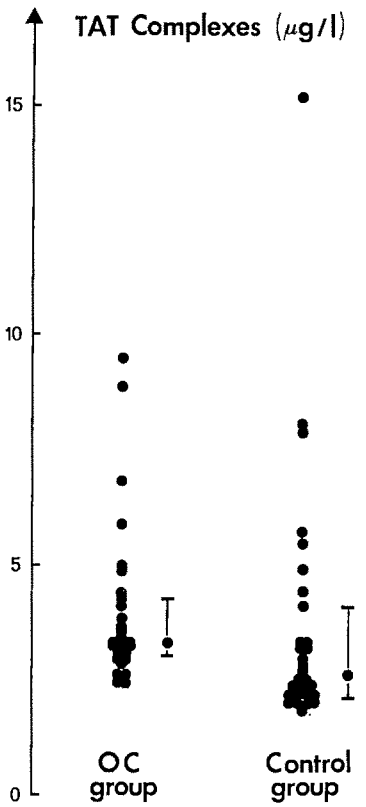


Fig. 1. Individual plasma concentrations of thrombin–antithrombin III *(TAT)* complexes (μg/L) in 28 healthy women taking oral contraceptives low in estrogen (OC group) and in 30 healthy women (control group). Median and 25 to 75 interpercentile ranges are indicated. Concentrations of thrombin–antithrombin III complexes were significantly higher in the oral contraceptive group ($p < 0.01$).

Results

The plasma concentrations of thrombin–antithrombin III complexes (Fig. 1) were significantly increased in the oral contraceptive group compared with nonusers ($p < 0.01$). Similarly, the plasma activities of tissue-type plasminogen activator were significantly increased ($p < 0.01$) and the plasma activities of plasminogen activator inhibition were significantly depressed ($p < 0.01$) in the oral contraceptive group compared with the control group (Fig. 2). Consistent with these latter results we observed significantly increased plasma concentrations of fibrin degradation products (Fig. 3) in the oral contraceptive group compared with nonusers ($p < 0.05$).

When we determined the ratio of thrombin–

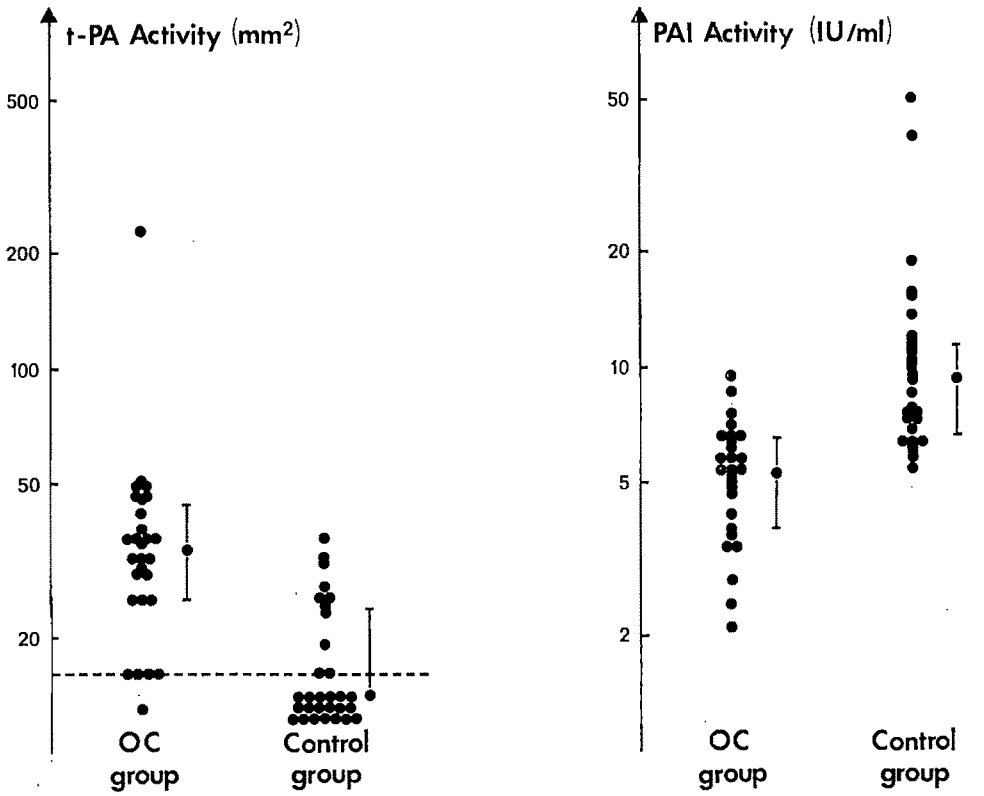


Fig. 2. Individual activities in plasma euglobulins of tissue-type plasminogen activator *(t-PA; left panel)* expressed as mm^2 (log scale; the detection limit of the fibrinogen batch used indicated by *horizontal broken line*) and plasminogen activator inhibition *(PAI; right panel)* expressed as IU/ml in 28 healthy women receiving oral contraceptives low in estrogen (OC group) and in 30 healthy women (control group). Medians and 25 to 75 interpercentile ranges are indicated. Activities of tissue-type plasminogen activator were significantly increased ($p < 0.01$), and activities of plasminogen activator inhibition significantly depressed ($p < 0.01$) in the oral contraceptive group.

antithrombin III complexes/fibrin degradation products (Fig. 4), a calculated measure of the actual, dynamic state of the hemostatic balance in an individual, we found no significant deviations between the two groups.

Twelve of the 28 women using oral contraceptives were light smokers, that is, less than 15 cigarettes per day, whereas the remaining 16 women were nonsmokers (Table I). When we compared the plasma levels of thrombin–antithrombin III complexes, tissue-type plasminogen activator activity, plasminogen activator inhibition activity, fibrin degradation products and the ratio of thrombin–antithrombin III complexes/fibrin degradation products between these two groups, we found no significant differences (Table II).

Comment

In accordance with conclusions from previous studies on the effect of oral contraceptives on the hemostatic system,[5, 6, 16-22] the present study indicates that oral contraceptives containing 30 to 50 μg of ethinyl estradiol induces significant changes in components involved in the activation of coagulation and fibrinolysis. We have observed increased plasma concentrations of thrombin–antithrombin III complexes (Fig. 1), increased plasma activities of tissue-type plasminogen activator (Fig. 2), decreased plasma activities of plasminogen activator inhibition (Fig. 2), and increased plasma concentrations of fibrin degradation products (Fig. 3) compared with control subjects. As a supplement to previous studies, these findings strongly suggest that the use of low-dose oral contraceptives in healthy women causes an enhanced generation of thrombin, an enhanced formation of fibrin, and an enhanced resolution of fibrin. However, using molecular markers for the evaluation of the relative activation of coagulation (thrombin–antithrombin III complexes) and fibrinolysis (fibrin degradation products), we found that the ratio of thrombin–antithrombin III complexes/fibrin degradation products did not deviate significantly between oral contraceptive users and control subjects (Fig. 4). These findings indicate a more rapid

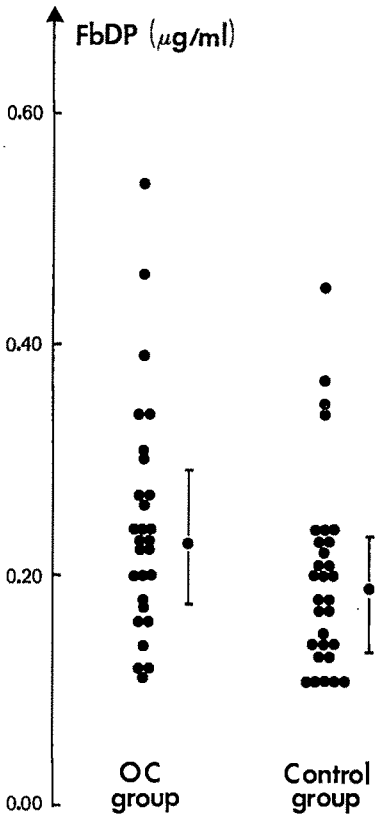


Fig. 3. Individual plasma concentrations of fibrin degradation products *(FbDP)* in 28 healthy women receiving oral contraceptives low in estrogen (OC group) and in 30 healthy women (control group). Medians and 25 to 75 interpercentile ranges are indicated. Concentrations of fibrin degradation products were significantly increased in the oral contraceptive group ($p < 0.05$).

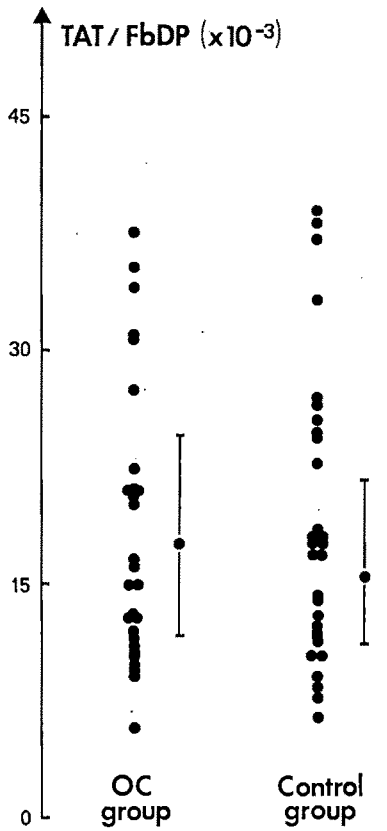


Fig. 4. Individual ratio of thrombin–antithrombin III complexes/fibrin degradation products *(TAT complexes/FbDP)* in 28 healthy women receiving oral contraceptives low in estrogen (OC group) and in 30 healthy women (control group). Medians and 25 to 75 interpercentile range are indicated. There was no significant difference between the two groups.

turnover of fibrinogen/fibrin among oral contraceptive users, whereas the balance between activation of coagulation and fibrinolysis is not significantly affected. Thus our study may help to explain the very low overall incidence of thromboembolic events in women using oral contraceptives despite obvious biochemical changes in individual components involved in hemostasis. It should be noted that light cigarette smoking, that is, less than 15 cigarettes per day, did not significantly affect changes in activation and fibrinolysis induced by oral contraceptives (Table II). This observation is compatible with a recent epidemiologic follow-up study,[23] which suggests a very moderate increased risk of cardiovascular death in oral contraceptive users smoking less than 15 cigarettes per day.

Although the observations reported here do not definitely explain the apparent association between the risk of thrombosis and the consumption of oral contraceptives, they point to the absence of an increased risk with respect to the effect on the hemostatic balance in normal women. The use of molecular markers in future studies would help elucidate whether a risk group is characterized by an enhanced generation of thrombin or a defective resolution of fibrin.

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PERSONAL, PRACTICAL ASPECTS SEEN FROM THE FAMILY PLANNING CLINIC'S POINT OF VIEW

Oral contraceptives in risk groups: Exclusion or monitoring?

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Careful consideration of absolute and relative contraindications, including newly appreciated factors such as past pregnancy-related hypertension, is essential to select what is termed the "safer women." A family history of either arterial or venous thrombosis indicates preliminary blood analysis to exclude atherogenic lipid states and thrombophilias. The goal then is to prescribe "safer pills." One should also allow for biologic variation in pharmacokinetics and end-organ responses. This can be done to a limited extent in clinical practice by using bleeding from the uterus as a "threshold bioassay." Namely, by identifying for each woman the lowest dose of a chosen estrogen-progestogen combination that is just sufficient to prevent breakthrough bleeding. Thereafter, monitoring requires attention to the development of new risk factors, regular blood pressure checks, and specific attention to the important side effects of headaches and migraines, especially if there are focal (cerebral ischemic) symptoms. (Am J Obstet Gynecol 1990;163:443-6.)

Key words: Oral contraceptive risk factors, breakthrough bleeding, lipid and hemostatis variables, focal migraine, blood pressure

Despite 30 years of research, the area of epidemiology, which gives the most relevant data about beneficial and adverse effects, provides mainly information about yesterday's pills and is too imprecise a tool to distinguish between formulations. Consequently, we are forced to give more weight than is warranted to minor differences in the effects on metabolic variables.

There are many pitfalls. Are the differences (especially in cross-sectional studies) from the pills studied or the characteristics of the women using them because of factors such as prescriber bias? If truly pill related, we still do not know the health implications of most of the observed changes. In situations in which we believe that we do, we must look at the whole picture, consider hemostasis as well as lipids, and measure blood pressure and blood constituents. In comparing different formulations, we may find benefits that are mutually exclusive (e.g., relatively estrogen-dominant pills may appear better for lipids but worse for changes to the hemostatic system). The fact that *mean* alterations are within the normal range may be falsely reassuring for some individuals, who may have significant abnormalities before they first take the combined oral contraceptive or have a major change within the range.

In short, we badly need more large comparative studies with a defined power great enough to avoid missing real differences, separate analyses of the extreme percentiles, comparative studies with randomization to formulations containing the older and new progestogens, and all with good statistical analysis. Also important is clinical judgment, which gives appropriate weight to the findings compared with those from other research (e.g., into carcinogenesis).

In clinical practice it is impractical to perform complex laboratory tests on allcomers. Fortunately, however, it is probable that the metabolic differences between the currently recommended lowest dose oral contraceptives are relatively unimportant, and all are acceptable for the average woman requesting this method. More good can probably be done by careful prescribing and appropriate monitoring than by overattention to metabolic minutiae.

In selected cases laboratory tests become relevant. As will be described, the signal for arranging them is mainly careful identification of clinical risk factors from personal and family history.[1,2]

Prescribing summary

In using the scheme that follows, risk-benefit analysis must closely involve the woman, a woman-centered approach. After counseling many women will consider that the known benefits (contraceptive and noncontra-

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6/0/20309

Table I. Risk factors for cardiovascular system disease[1]

Risk factor	*Absolute contraindication*	*Relative contraindication*	*Remarks*
FH of CVS disease (arterial or venous) in a first-degree relative ≤45 yr	Known atherogenic lipid profile or prothrombogenic hemostatic profile or tests not available	Normal blood profiles or first attack in relative >45 yr	Normal blood if FH of arterial disease must test BOTH for lipids and hemostasis
DM	Severe or diabetic complications present (e.g., retinopathy)	Not severe/labile and no complications; young patient with short duration of DM	POP usually better choice hormone method
Raised BP	Systolic BP >160, diastolic BP >95 mm Hg, on repeated testing	Systolic 130-160; diastolic BP, 85-95 mm Hg	POP better choice
Cigarette smoking	>40 cigarettes/day	5-40 cigarettes/day	
Increasing age	>45 nonsmokers	35-45 non-smokers	Smokers should avoid/discontinue COCs 10 yr earlier
Excess weight	>50% above ideal for height	20%-50% above ideal	

Modified with permission. In: Filshie M, Guillebaud J, eds. Contraception science and practice. London: Butterworths, 1989:71.

FH, Family history; *CVS*, cardiovascular system; *DM*, diabetes mellitus; *POP*, progestogen-only pill; *BP*, blood pressure; *COC*, combined oral contraceptive.

Some of the numbers selected are necessarily a little arbitrary and relate to use of COCs solely for contraception.

Use of COCs for medical indications entails a different risk-benefit analysis, often more favorable to the use of the COC (see text).

Past personal history of any CVS disease/disorder associated with or predisposing to thrombosis (arterial or venous) always absolutely contraindicates the method.[1]

Synergism: Two or more relative contraindications signifies that the COC is absolutely contraindicated.

Recommendation on October 26, 1989, of Fertility and Maternal Health Drugs Advisory Committee to the FDA that there should be *no upper age limit* for COC use by *healthy nonsmoking* women makes age 45 years per se no longer an absolute contraindication.

ceptive) outweigh the known *and likely unknown* risks. Others will decide against the method in favor of an alternative, which is their prerogative.

The goal is to treat what I call the safer women with the safer pills. This involves answering four questions[2]:

1. Who never? (absolute contraindications)
2. Who usually not? (perhaps, but will special advice and monitoring—relative contraindications)
3. Which pill?
4. Which second choice of pill?

"The pill is reasonably safe: Some women are dangerous"

The absolute and relative contraindications to cardiovascular disease are listed in Table I; the remainder are described elsewhere.[1] Table I also suggests the point at which each of the recognized risk factors might pose sufficient risk on its own for the contraindication to be considered absolute rather than relative. The presence of two or more risk factors of a lesser degree implies synergism in decision making, which again is an absolute contraindication to the method in most cases.[1]

Family history of an arterial incident in a first-degree relative under age 45 years (especially a nonsmoker) indicates full blood lipid analysis (if available). Once identified, it is well accepted that preexisting atherogenic lipid profiles absolutely contraindicate the combined oral contraceptive for that individual.

Less developed in combined oral contraceptive prescribing practice and yet equally relevant is the concept of the thrombophilias. The most common of these prothrombotic congenital disorders are deficiencies in antithrombin III, protein C, or protein S. Together with rarer similar disorders so far characterized, they occur in about 1:2500 prospective pill takers[3] compared with a rate of about 1:500 for familial hypercholesterolemia.[4] Once again family history provides the clinical clue. An episode of venous or arterial thrombosis (more often the former) in a close relative under the age of 40 to 45 years indicates referral for investigation, ideally to a center capable of performing these tests. I believe that selective application of such specific tests to this relevant minority, chosen by family or personal history of thrombosis, would be more valuable than to arrange routine clotting tests or nonselective screening.

Migraine

Migraine is a specific risk factor for thrombotic stroke. In his monograph Bickerstaff[5] identified a group of young women admitted with strokes who had

Table II. Reasons to stop estrogen, pending advice

Symptoms	*Worst diagnosis or risk*
Pain	
In calf	DVT
In chest	PE, myocardial infarction
In abdomen	Thrombosis of major vessel
Dyspnea/hemoptysis	Pulmonary embolus
Migraine	
± Loss of visual field	Retinal thrombosis, impending stroke
± Unilateral numbness	Impending stroke
± Unilateral weakness	Impending stroke
± Dysphasia	Impending stroke
± Unexplained collapse	Impending stroke
BP ≥160/95	Hemorrhagic stroke
Immobilization after accident or emergency surgery	DVT/PE
Jaundice	Cholestasis or hepatitis

DVT, Deep venous thrombosis; *PE,* pulmonary embolus; *BP,* blood pressure.

had focal migraines. They had experienced attacks, during which lateralizing neurologic sypmtoms occurred attributable to transient cerebral ischemia (Table II). Estrogen in the combined pill was continued, and the transient ischemia tragically became permanent. A controlled trial would be unethical, and therefore prudence dictates that focal symptoms before or during pill taking should lead to discontinuation or permanent avoidance of the combined oral contraceptive in the future. The same applies to severe, sustained, or "crescendo" migraines. Diffuse migraine headaches, with which the women can live, may be considered a relative contraindication, provided that the woman is educated about the need to report any future transient ischemic symptoms[1] (Tables II and III).

Pregnancy-related hypertension (toxemia)

Croft and Hanneford[6] have recently shown from data derived from the British Royal College of General Practitioners' Study that a history of toxemia during pregnancy increased the risk of subsequent myocardial infarction (adjusted risk ratio, 2.8). If such women also smoked, the relative risk rose to 41. Use of the combined oral contraceptive had no multiplicative effect, and indeed current use of birth control pills increased the risk only among women who also smoked. Nevertheless, prudence dictates that any past history of severe pregnancy-related hypertension should be carefully noted. If combined with the risk factors in Table I, in the future it should be considered a "strong" relative contradindication to adding the combined oral contraceptive.

Safer pills

This meeting has attempted to identify these safer pills. I will not try to define the "best buy." However, it appears from recent research that the safer pills are "smaller": in almost all cases the estrogen dose should be 35 μg or less, and the minimum *acceptable* amount of selected progestogen should also be used. It also seems that the so-called "third-generation" progestogens in the doses available produce less potentially adverse changes in lipids, while not apparently causing more effects on hemostasis than available norethindrone or levonorgestrel varieties with the same estrogen dose. They also have a relatively low rate of breakthrough bleeding and other problems with the pill cycle. This is significant in regard to the word "acceptable."

Most would accept the dictum of Professor Victor Wynn: "If we can measure any substance in a pill-user, we would like it to be normal, or as near normal as possible." The most significant changes in circulatory disease are those affecting lipoproteins, the renin-angiotensin system, and coagulation. The liver is intimately involved in all these areas of metabolism. It appears that many of the pill's problems relate to its being a pill: far less impact is given to the liver if the same hormones are given by nonoral routes. However, for now we do not have these contraceptive alternatives in most countries.

Individual variation

Many researchers have shown the wide variation in both estrogen and progestogen pharmacokinetics that exists between individuals, which is associated with more than a 10-fold variability in blood levels.[7] There is similar variation in end organs. Far too little notice is taken in routine prescribing. It is futile to expect one dose level of a given estrogen-progestogen to suit all women. Ahluwalia et al.[8] showed a statistically significantly higher level of ethinyl estradiol in hypertensive pilltakers than in nonhypertensive women taking the same pills. In a major study at the Margaret Pyke Centre, we are attempting to confirm this and also to correlate a wide range of metabolic changes in blood levels of exogenous hormones. Many women could receive long-term higher doses than needed for satisfactory contraception and cycle control, consequently with greater risk of metabolic abnormalities and minor or major side

Table III. When to report if you have side effects[9]

Minor side effects should be mentioned at your next appointment
See the doctor at once if you have any of these:
- Painful swelling in the leg
- Severe pain in the chest or stomach
- Breathlessness or coughing with blood
- A bad fainting attack or collapse
- Unusual headaches, difficulty with speech/sight
- Numbness or weakness of a limb

effects, and only because no attempt was made to try a lower dose. The question is, how do we avoid giving the woman who tends to have the highest blood levels a stronger formulation than she really requires?

Breakthrough bleeding is an annoying symptom. When it occurs, it may be caused by low blood levels (witness the effect of an interacting drug such as rifampicin). However, even if lack of endometrial stability results from features of that end organ, it is still logical not to prescribe any more hormone than the minimum to give a good cycle. I have argued in more detail elsewhere that one should attempt to give each pilltaker the lowest dose of a selected estrogen-progestogen that the uterus allows,[1,2] with bleeding used as a "threshold bioassay." Manufacturers would help in this endeavor if they would provide different dose levels for the newer progestogens, such as those that already exist for norethindrone and levonorgestrel pills (i.e., a "ladder").[2]

Monitoring

After patients with absolute contraindications are excluded, those with risk factors identified, and a pill chosen that has the least biologic impact and is just above the threshold for cycle control, what should be done about monitoring?

In some patients in whom there are medical indications (e.g., treatment of endometriosis, to avoid hysterectomy with its associated risk, or when a disease is present that may deteriorate markedly in pregnancy), greater risk may be tolerated. Such women, along with those who have a solitary risk factor (Table I) interpreted as no more than a relative contraindication, still require careful monitoring for the development of any new risk factor. The rest need less supervision: the most essential factor is regular blood pressure checks, combined with ready access to the prescribing clinician. All pilltakers should be informed of those symptoms that should lead them to take urgent advice (Table III).[9]

Blood pressure

I believe that this is the single most important test for the ongoing safety of the pill. Insurance Company studies have shown for populations that increased blood pressure adversely affects life expectancy through cardiovascular disease, with no apparent threshold.[10] Prudence dictates that although its mechanism may differ, combined oral contraceptive–related hypertension is taken to have similar importance. Prescribers have often remarked how helpful it would be if there were some office test of safety, some special reagent that could be added to a body fluid such as urine, which would turn it "red" if the woman should discontinue taking the pill but "green" if she could safely continue to take it. I maintain that the development of combined oral contraceptive–related hypertension can be used in this way. If, for example, a 33-year-old smoker is found to have a blood pressure of 140/90 on repeated testing, this means that she should now use another birth control method (and not wait until the age limit of 35 years when all smokers should discontinue use of the pill). It is a "pink" test.

In conclusion, no one should be under any pressure to use oral contraception. The aim of good counseling is to provide sufficient information and advice so the woman fully exercises her right to consent to treatment, considers the alternatives, and assumes acceptable risks in life generally. I feel that it is essential to back up counseling with appropriate literature: leaflets, such as those already mentioned,[9] or a practical "handbook for the owner-driver"[11] for those patients seeking additional information.

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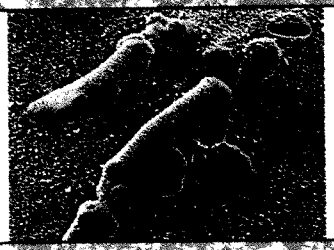
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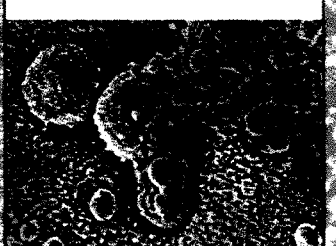
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BEFORE
Scanning electron micrograph (×3300) of *Candida albicans* grown for 48 hours on agar.

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Femstat Prefill destroys the integrity of the yeast cell.



AFTER
Scanning electron micrograph (×3300) of *Candida albicans* on agar plate with butoconazole nitrate.

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■ Microbiological cure rates in 95% of patients eight days following Femstat three-day therapy.[1]

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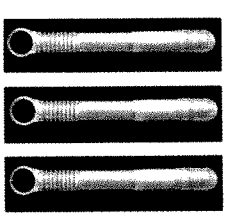
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■ A low incidence of reported adverse reactions.[2]

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(butoconazole nitrate) VAGINAL CREAM 2%

3-day† victory over vulvovaginal candidiasis

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Information for the Patient: Do not discontinue prematurely during menstruation or because of symptomatic relief.

Carcinogenesis: Animal studies have not been done.

Mutagenesis: Mutagenicity studies were negative.

Impairment of Fertility: Animal studies showed no impairment of fertility.

Pregnancy Category C: Adverse effects were noted in animals treated with high oral doses. No studies were done in women during first trimester. Patients in the second or third trimester have shown no adverse effects attributable to the drug.

Nursing Mothers: Use with caution.

Pediatric Use: Safety and efficacy have not been established.

ADVERSE REACTIONS: Vulvar/vaginal burning in 2.3% of patients, vulvar itching in 0.9%, discharge, soreness, swelling, itching of fingers each in 0.2%. Complaints caused 1.6% to discontinue drug.

DOSAGE AND ADMINISTRATION: Non-pregnant Patients: The recommended dose is one applicatorful of cream (approximately 5 grams) intravaginally at bedtime for three days. Treatment can be extended for an additional three days if necessary.

Pregnant Patients (second and third trimesters only): The recommended dose is one applicatorful of cream (approximately 5 grams) intravaginally at bedtime for six days.

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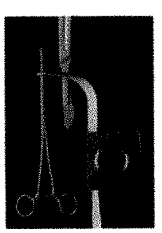
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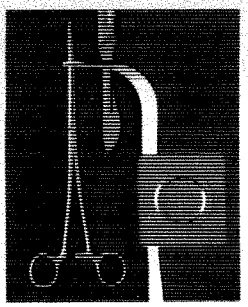
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In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, Briceland LL, Cooper B. The conversion of cefoxitin usage to cefotetan: an interdisciplinary approach. *Am J Surg.* 1988; 155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT. Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg.* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference.* ed 43. Oradell, NJ: Medical Economics Co; 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH. Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg.* April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, Outman WR, Deckers PJ, Martens MG. Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg.* 1988;155(5A):67-70. **7.** Centers for Disease Control. 1989 Sexually Transmitted Diseases Treatment Guidelines. *MMWR.* 1989;38(suppl S-8):1-43.

Please see adjacent page for brief summary of prescribing information.

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Count on

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(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus.**
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.
NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.
INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.
DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.
USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.
IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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Stephen J. Carlan, MD, Peter Papenhausen, PhD, William F. O'Brien, MD, Marcello Pietrantoni, MD, Ronald A. Chez, MD, and Pamela Stephens, RN
Tampa, Florida

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Tomoaki Ikeda, MD, and Norimasa Mori, MD
Miyazaki, Japan

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Mohammad R. Rajabi, MD, David D. Dean, PhD, and J. Frederick Woessner, Jr., PhD
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Peter R. Garner, MD, Mary E. D'Alton, MD, Denis K. Dudley, MD, Pierre Huard, MD, and Michael Hardie, MD
Ottawa, Ontario, Canada

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Joseph M. Tibaldi, MD, Daniel L. Lorber, MD, and Alan Nerenberg, MD
Flushing, New York

Diabetic ketoacidosis and transient severe insulin resistance developed in a pregnant woman with diabetes who was treated with subcutaneous terbutaline infusion tocolysis.

A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis 510
Fabio Barbone, MD, DrPH, Harland Austin, DSc, William C. Louv, PhD, and W. James Alexander, MD
Birmingham, Alabama

A clinical trial demonstrated that spermicide slightly reduces the incidence rate of trichomoniasis and bacterial vaginosis and that oral contraceptive use strongly protects against trichomoniasis.

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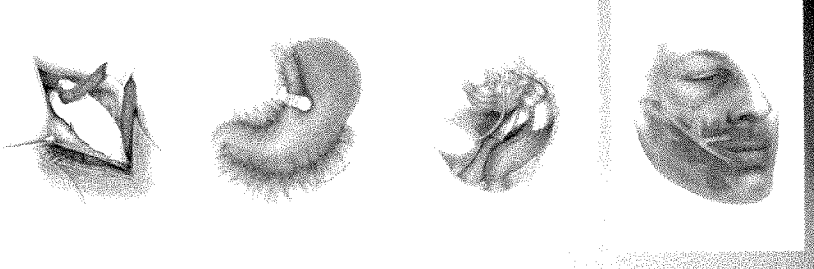
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Charles H. Livengood III, MD, Jessica L. Thomason, MD, and Gale B. Hill, PhD
Durham, North Carolina, and Milwaukee, Wisconsin

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Howard L. Minkoff, MD, Sandra McCalla, MD, Isaac Delke, MD, Roy Stevens, MD, Martin Salwen, MD, and Joseph Feldman, DrPH
Brooklyn and Albany, New York

A blinded urine and serum survey among parturients at an inner city hospital revealed an association between cocaine metabolites in urine and serologic evidence of syphilis and human immunodeficiency virus.

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Memphis, Tennessee

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Prato and Milan, Italy

A rare case of postpartum coronary artery dissection was successfully treated by heart transplantation.

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Paris, Romainville, Bordeaux, Pessac, Villeneuve St. Georges, Pontoise, Lyon, Strasbourg, and Cherbourg, France, and Bloemfontein and Durban, South Africa

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Jay H. Levin, MD, Maria Lacarra, RN, Gerrit d'Ablaing, MD, David A. Grimes, MD, and Michael Vermesh, MD
Los Angeles, California

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Joseph C. Gambone, DO, Robert C. Reiter, MD, Joel B. Lench, MD, and J. George Moore, MD
Los Angeles and San Diego, California, and Iowa City, Iowa

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R. Edward Varner, MD
Birmingham, Alabama

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Jim van Eyck, PhD, Karin van der Mooren, MD, and Juriy W. Wladimiroff, PhD
Rotterdam, The Netherlands

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Leon G. Smith, Jr., MD, Robert J. Carpenter, Jr., MD, Whitney Gonsoulin, MD, Giancarlo Mari, MD, Alexander A. Reiter, MD, Frank Greenberg, MD, and Carolyn Powell, RN, BSN
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London, England, and Groningen, The Netherlands

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New York, New York, and Monmouth, New Jersey

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Neal S. Rote, PhD, Dorene Dostal-Johnson, MS, and D. Ware Branch, MD
Scarborough and Portland, Maine, and Salt Lake City, Utah

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Louisville, Kentucky

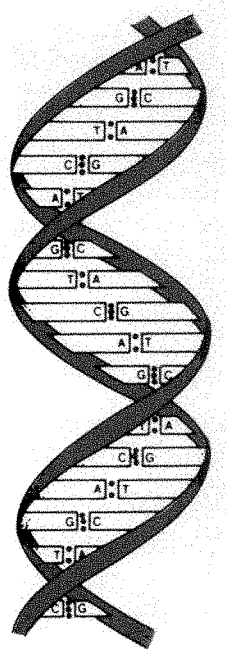
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Irwin Goldstein, MD, Gilbert J. Wise, MD, and M. Leon Tancer, MD
Brooklyn, New York

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Vivigen Introduces Cystic Fibrosis Testing



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Rotterdam, The Netherlands

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Cambridge and Boston, Massachusetts

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Nottingham, England

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Hidetaka Izumi, MD, Jirou Ichihara, MD, Yoshio Uchiumi, MD, and Koichi Shirakawa, MD

Fukuoka, Japan

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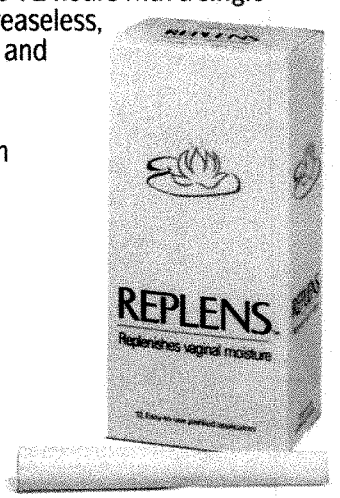
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ORAL CONTRACEPTIVE AGENTS: BRIEF SUMMARY

DESCRIPTION

TRI-NORINYL 21-DAY Tablets provide an oral contraceptive regimen of 7 blue tablets followed by 9 yellow-green tablets and 5 more blue tablets. Each blue tablet contains norethindrone 0.5 mg and ethinyl estradiol 0.035 mg and each yellow-green tablet contains norethindrone 1 mg and ethinyl estradiol 0.035 mg.

TRI-NORINYL 28-DAY Tablets provide a continuous oral contraceptive regimen of 7 blue tablets, 9 yellow-green tablets, 5 more blue tablets, and then 7 orange tablets. Each blue tablet contains norethindrone 0.5 mg and ethinyl estradiol 0.035 mg, each yellow-green tablet contains norethindrone 1 mg and ethinyl estradiol 0.035 mg, and each orange tablet contains inert ingredients.

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use these products as a method of contraception.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who have the following conditions: Thrombophlebitis or thromboembolic disorders • A past history of deep vein thrombophlebitis or thromboembolic disorders • Cerebral vascular or coronary artery disease • Known or suspected carcinoma of the breast • Carcinoma of the endometrium, and known or suspected estrogen-dependent neoplasia • Undiagnosed abnormal genital bleeding • Cholestatic jaundice of pregnancy or jaundice with prior pill use • Hepatic adenomas, carcinomas or benign liver tumors • Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, hypercholesterolemia, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations containing 0.05 mg or higher of estrogen. The effects of long-term use with lower dose formulations of both estrogens and progestogens remain to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease. Relative risk, the *ratio* of the incidence of a disease among oral contraceptive users to that among non-users, cannot be assessed directly from case control studies, but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6. The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women 35 or older, with smoking accounting for the majority of excess cases.

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors for coronary artery disease, such as hypertension, diabetes, hyperlipidemias, hypercholesterolemia, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and impair oral glucose tolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see **WARNINGS,** section 9). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. One cohort study has shown the relative risk to be somewhat lower, about 3 for new cases (subjects with no past history of venous thrombosis or varicose veins) and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A 2- to 6-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery and during and following prolonged immobilization. Since the immediate postpartum period also is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular diseases

An increase in both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. In general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users for both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk also is greater in women 35 or older and among smokers.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with some progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content that produces satisfactory results for the individual.

e. Persistence of risk of vascular disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. Subarachnoid hemorrhage also has a significantly increased relative risk after termination of use of oral contraceptives. However, these studies were performed with oral contraceptive formulations containing 0.05 mg or higher of estrogen.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's—but not reported in the U.S. until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

3. CARCINOMA OF THE BREAST AND REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use. A few studies have shown a slightly increased relative risk of developing breast cancer, although the methodology of these studies, which included differences in examination of users and non-users and differences in age at start of use, has been questioned. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast or cervical cancers, a cause and effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) oral contraceptive users. However, these cancers are extremely rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is less than 1 per 1,000,000 users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. More recent studies do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to impair oral glucose tolerance. Oral contraceptives containing greater than 0.075 mg of estrogen cause glucose intolerance with impaired insulin secretion, while lower doses of estrogen may produce less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS**, sections 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives. The incidence of risk also was reported to increase with continued use and among older women. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. PHYSICAL EXAMINATION AND FOLLOW-UP

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines.

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. CARCINOGENESIS

See **WARNINGS** section.

10. PREGNANCY

Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

INFORMATION FOR THE PATIENT

See **PATIENT LABELING.**

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section): Thrombophlebitis • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas, carcinomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis • Retinal thrombosis

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema • Melasma which may persist • Breast changes: tenderness, enlargement, secretion • Change in weight (increase or decrease) • Change in cervical erosion and secretion • Diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine • Rash (allergic) • Mental depression • Reduced tolerance to carbohydrates • Vaginal candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome • Cataracts • Changes in appetite • Cystitis-like syndrome • Headache • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Vaginitis • Porphyria • Impaired renal function • Hemolytic uremic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

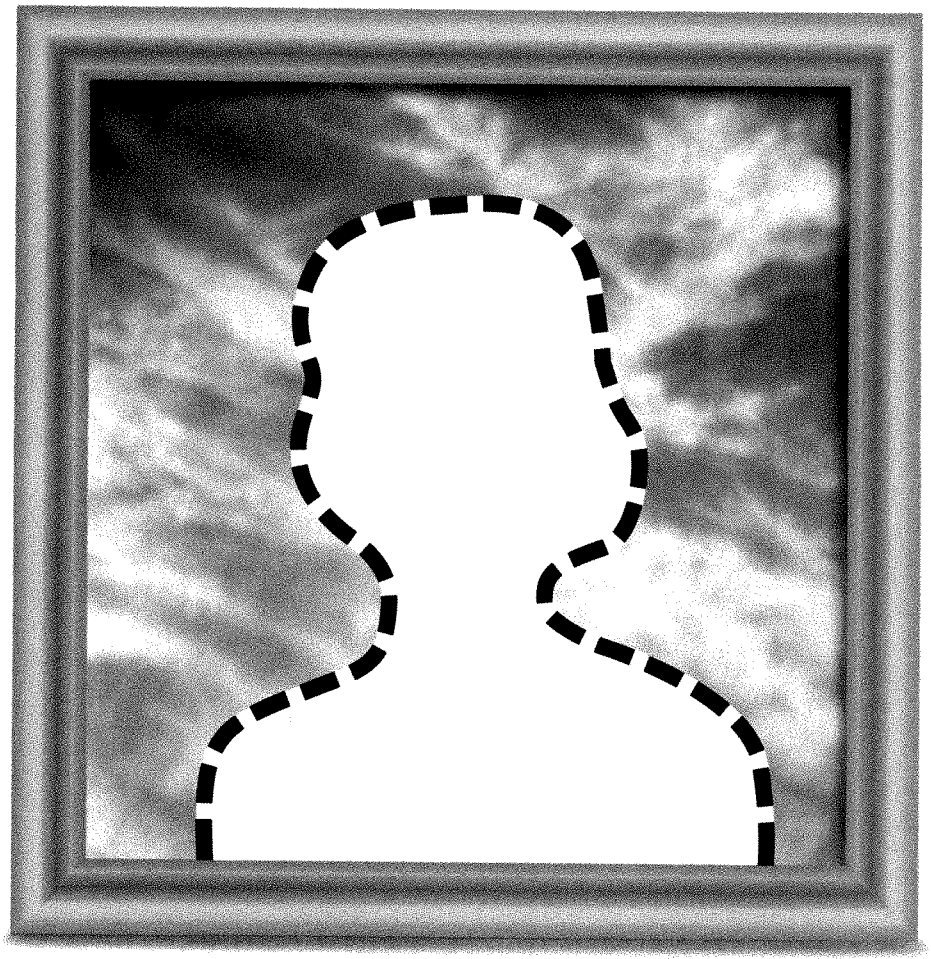
Effects on menses: • Increased menstrual cycle regularity • Decreased blood loss and decreased incidence of iron deficiency anemia • Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation: • Decreased incidence of functional ovarian cysts • Decreased incidence of ectopic pregnancies

Effects from long-term use: • Decreased incidence of fibroadenomas and fibrocystic disease of the breast • Decreased incidence of acute pelvic inflammatory disease • Decreased incidence of endometrial cancer • Decreased incidence of ovarian cancer

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The requirements for manuscripts submitted to the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" established by the International Committee of Medical Journal Editors and published in *Annals of Internal Medicine* 1988;108:258-65. Certain requirements unique to our JOURNAL are provided in Information for Authors, published in each issue of the JOURNAL.

Manuscript submission. Manuscripts should be submitted to one of the three Editors as follows:

1. **Dr. Brewer**—all manuscripts originating from the southeastern quadrant of the United States or Canada and those presented before one of the official sponsoring societies, except the Society for Gynecologic Investigation and The Society of Perinatal Obstetricians.

2. **Dr. Zuspan**—manuscripts from the northeastern quadrant of the United States and from Japan, Israel, Italy, and England, manuscripts written for Clinical Opinion and Current Development, and Letters to the Editors. Dr. Zuspan is responsible for manuscripts from The Society of Perinatal Obstetricians. Manuscripts from The Society of Perinatal Obstetricians should be submitted to Dr. Donald R. Coustan, Department of Obstetrics and Gynecology, Women and Infants Hospital of Rhode Island, 101 Dudley St., Providence, RI 02905.

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CLINICAL SECTION

Clinical Opinion

Prenatal diagnosis of congenital cytomegalovirus infection: Two decades later

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Cytomegalovirus is the most common cause of congenital infection in the United States, yet there has been little progress in the prenatal diagnosis of this intrauterine infection. We present evidence that viral culture of amniotic fluid may be a useful adjunct procedure, when performed as part of the antenatal evaluation of suspected fetal cytomegalovirus infection. (AM J OBSTET GYNECOL 1990;163:447-50.)

Key words: Cytomegalovirus, prenatal diagnosis, congenital infection

Cytomegalovirus (CMV) is the most common cause of congenital infection, affecting 30,000 to 40,000 live-born infants annually in the United States.[1,2] However, prenatal diagnosis of fetal CMV infection has received little attention over the last 20 years and was not mentioned in a recent editorial strongly urging renewed efforts to eliminate the problem.[3] In this Clinical Opinion, we briefly survey the epidemiologic characteristics of congenital CMV infection. Then we review published methods of prenatal diagnosis and provide evidence for our opinion that viral cultures of amniotic fluid may be a useful procedure. Finally, we suggest that antenatal diagnosis can play an important role in suggested programs that seek to prevent congenital infection and to treat those cases that do occur.

CMV is one of the human herpesviruses, which also include herpes simplex virus types 1 and 2, varicella-zoster virus, Epstein-Barr virus, and human herpesvirus type 6. Pregnant women usually acquire the initial CMV infection by exposure to body excretions (saliva, urine) of young children or by intimate sexual contact.[1-3] Women at greatest risk are those <25 years old and those with young children in the home.[4] Women who contract the infection often have a subclinical course; a small number manifest a mononucleosis-like syndrome 4 to 8 weeks later, which is characterized by fever, splenomegaly, thrombocytopenia, and atypical lymphocytosis. If the virus first enters via the nasopharyngeal or oropharyngeal route, it next spreads to the salivary glands, where it replicates before gaining access to the maternal circulation. During the viremic phase, the virus may localize in the fetus of a pregnant woman.

The risk of fetal infection is likely the same throughout pregnancy, but its destructive potential is greatest after primary maternal infection in the first half of gestation.[1,2] It is estimated that CMV will be transmitted to 50% of fetuses after primary infection and that 10% of these infants will be clinically affected.[1,2] The number of severely damaged infants has been estimated between 1500 and 4000 per year.[1-3] Many congenitally infected infants will appear normal at delivery but manifest delayed neurologic sequelae. The mechanism of CMV transmission to the fetal tissues has not been thoroughly eludicated, but transmission may occur hematogenously when infected leukocytes traverse the placental barrier to reach the fetal circulation via the um-

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Table I. Prenatal diagnosis of CMV infection by amniocentesis

Reference No.	*Year*	*Maternal symptoms and date*	*Prenatal ultrasonography*	*Date (wk) at amniocentesis*	*Fetal outcome*
5	1971	CMV mononucleosis at 8 wk	No	21	Abortion at 22 wk. Inclusion bodies in pancreas, lungs, liver, kidneys; no congenital anomalies
6	1981	CMV hepatitis at 12 wk	No	36	Term newborn. Undescended testis; right equinovarus; hypotonia
7	1982	None	IUGR	32	Term newborn. Severe congenital CMV syndrome (IUGR, microcephaly, hepatosplenomegaly, intracerebral calcifications, jaundice, thrombocytopenia)
8	1984	Flu syndrome at 10 wk	Polyhydramnios, fetal ascites	33	Premature newborn (33 wk). Ascites, microcephaly, hepatosplenomegaly, hypoplastic lungs, thrombocytopenia. Autopsy results: inclusion bodies in liver, kidneys, pancreas; cerebral ventriculomegaly
8	1984	None	IUGR and microcephaly	25	Abortion at 30 wks. No congenital anomalies
9	1986	None	Cerebral ventriculomegaly, posterior fossa cyst	36	Newborn (37 wk). Severe congenital CMV syndrome (hepatosplenomegaly, intracerebral calcifications, diffuse brain atrophy, dilated cisterna magna)
10	1988	None	Fetal ascites	28	Preterm newborn (36 wk). Petechiae, hepatomegaly, thrombocytopenia, and respiratory difficulty
11	1988	None	Polyhydramnios, fetal hydrops, cerebral ventriculomegaly	28	Term newborn. Microcephaly; agenesis of corpus callosum; hepatomegaly; borderline IUGR
12	1990	Fever, loose stools, uterine tenderness at 37 wk	IUGR, right hydronephrosis, oligohydramnios	37	Term newborn. Caudate nucleus cyst; right hydronephrosis; borderline IUGR
12	1990	None	Pericardial effusion	23	Term newborn. No stigmas of congenital CMV infection

IUGR, Intrauterine growth retardation.

bilical cord vessels. However, other routes may be equally accessible to viral transmission. For instance, the virus may infect placental tissues first and then amniotic cells. Consequently, infected amniotic cells would be ingested by the fetus, after which virus could replicate in the oropharynx and invade the fetal circulation to reach target organs. The tubular epithelium within the kidney appears to be a major site of viral replication. By either mechanism of infection, the fetus would excrete CMV via urine into the amniotic fluid. The amniotic fluid therefore would seem a logical choice of bodily fluid for determination of fetal CMV status.

The first report of CMV isolation from the amniotic fluid was published in this JOURNAL in 1971.[5] Nine additional case reports of antenatally diagnosed CMV infection after amniocentesis are summarized in Table I.[6-12] In contradistinction to the positive findings chronicled in Table I, Stagno et al.[13] briefly mentioned three anecdotal cases in which viral cultures of amniotic fluid were negative even though CMV was isolated from the infants postnatally. Unfortunately, no further prenatal history was given, thus making interpretation difficult. In view of the well-documented neonatal course of congenital CMV infection were viruria is a constant finding, it is difficult to accept the negative findings of Stagno et al.[13] as commonplace. Taken together, the data in Table I strongly suggest that viral culture of amniotic fluid should be obtained in pregnant women

in whom primary CMV infection is suspected or documented. Likewise, CMV cultures may be indicated when ultrasonography reveals fetal problems such as intrauterine growth retardation, hydrops or ascites, and central nervous system abnormalities. In the cases cited in Table I, eight had abnormal findings on ultrasonographic examination of the fetus. In the remaining two cases, ultrasonography was not performed.

In addition to amniocentesis, other techniques have been applied toward the detection of fetal CMV infection. In 1982, Lange et al.[14] reported on a 28-year-old woman at 25 weeks of gestation who was found to have a hydropic fetus by ultrasonography. Pure fetal blood was obtained by fetoscopy. Total immunoglobulin M content in the serum was modestly elevated at 11 mg/dl. Radioimmunoassay for CMV-specific immunoglobulin M showed a high titer in fetal serum, as well as in maternal serum obtained at 21 weeks' gestation. At birth, CMV was isolated from the urine. In 1988 Hogge et al.[15] performed cordocentesis at 36 weeks of gestation on a pregnant woman whose fetus had sonographic evidence of severe hydrocephalus and unilateral hydronephrosis. They detected CMV-specific immunoglobulin M at a titer of 1:256 in the fetal blood sample. Because of severe fetal anomalies, labor was induced after cephalocentesis. (No CMV culture results were mentioned in the report.) Although cordocentesis has supplanted fetoscopy for fetal blood sampling and may be a preferred alternative to amniocentesis since more information can be obtained about the hematologic status,[16-18] amniocentesis is a more widely available procedure. For the above reasons, viral culture of amniotic fluid may be at the minimum a useful adjunct when fetal CMV infection is suspected. At the present time there is no information about isolation of CMV from amniotic fluid before 21 weeks of gestation (see Table I).

Why attempt any antenatal diagnosis? There are several reasons. First, it will aid in the study of the natural history of congenital CMV infection; e.g., the latest case in Table I describes for the first time a transient fetal abnormality (a pericardial effusion likely the result of pericarditis) associated with fetal infection. Second, asymptomatic neonates may develop sequelae in later life. Forewarned with knowledge of a congenital infection, family and health care workers will be better equipped at early detection of these sequelae. Third, antenatal diagnosis may allow identification of parameters that discriminate between those fetuses that are infected but fail to develop the congenital syndrome and those with severe sequelae; e.g., will the latter group persistently excrete virus into the amniotic fluid since they usually exhibit prolonged viruria postnatally? The fourth reason for antenatal diagnosis is the potential application of fetal therapy. Because of recent advances in monoclonal antibody technology, CMV cultures can now be read in 1 to 3 days rather than 1 to 3 weeks.[19] Thus results of the amniotic fluid cultures are quickly available to both physician and patient. With advances in viral chemotherapy, antenatal diagnosis of fetal CMV infection may lead to treatment of the mother with an antiviral agent known to cross the placenta. Ganciclovir has shown efficacy in treatment of CMV-induced retinitis and is currently being administered to newborn infants who were congenitally infected with CMV.[2, 3] Pathologically, treatment of the affected neonate is likely too late. Much of the virally induced damage to the infant may already have occurred before delivery. If intrauterine treatment were safe and effective, it would encourage routine CMV serologic screening to identify women at risk (those who lack CMV antibody at onset of pregnancy).[3] Similar therapeutic interventions have already been initiated for the prenatal treatment of fetal toxoplasmosis in regions where the infection is endemic.[20]

In conclusion, we concur that congenital CMV infection is a major health problem which has received inadequate attention. Though its precise sensitivity is unknown, amniotic fluid culture for CMV diagnosis is a useful adjunct, as illustrated by the 10 cases in Table I. The procedure can easily be performed as part of the prenatal evaluation of suspected congenital CMV infection.

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A chill wind blows: Webster, obstetrics, and the health of women

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The Supreme Court decision in *Webster v Reproductive Health Services* permits states to regulate abortion in fashions that may be medically unsound and may significantly restrict access. This decision challenges the contemporary practice of obstetrics and threatens to curtail access to needed services, particularly for poor women, who are at highest risk of pregnancy-associated medical complications and death. Governmental restrictions on abortion interfere with the obstetrician's basic goal of providing optimal care for the patient. Obstetricians dedicated to providing the best care to their patients should help to ensure that safe abortion be part of a spectrum of reproductive health care that is available to all American women. (AM J OBSTET GYNECOL 1990;163:450-2.)

Key words: Webster decision, abortion, maternal mortality, infant mortality, reproductive health

Justice Blackmun, in his dissenting opinion to the Supreme Court decision in the *Webster v Reproductive Health Services* case, wrote that: "I fear for the future.—For today—the women of this nation still retain the liberty to control their destinies. But the signs are evident and very ominous and a chill wind blows."[1] We concur with Justice Blackmun and fear that the chill wind blows most seriously for poor women, those most threatened by the Webster decision.

The decision effectively states that, short of prohibiting abortion within the first 24 weeks of gestation, a state may regulate performance of the procedure however it chooses, apparently even if that regulation is medically unsound and so encumbers the procedure as to significantly restrict access. The specific provisions that the State of Missouri has been permitted to enforce include prohibition on the use of public funds, facilities, and personnel for the performance of abortion, even if paid for by the patient, and inappropriate viability testing requirements.[2] In the latter case amniocentesis to measure the lecithin/sphingomyelin (L/S) ratio, for example, is not reliable as a measure of lung maturity until 30 gestational weeks or later. It is, in our opinion, medically contraindicated to recommend an invasive procedure, such as amniocentesis, when it is known that the results will not be informative or useful. Moreover, the court refused to rule on the preamble to Missouri's abortion law that declares that life begins at conception and defines conception as fertilization.

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The very shape of contemporary obstetrics is challenged, and future developments constricted, if the state's "compelling interest" in fetal life is extended back to the moment of fertilization. Prenatal diagnosis, for example, would become of limited value with diagnostic capabilities far exceeding therapeutic possibilities. Implicit in offering α-fetoprotein screening, chorionic villus sampling, amniocentesis for karyotyping, and other probes for specific fetal abnormalities is the option of termination of pregnancy. Without such an option, there is little rationale for carrying out these testing procedures.

Future developments in reproductive medicine are likewise restricted. Why explore low α-fetoprotein values as a screen for Downs syndrome or pursue prenatal diagnostic probes for cystic fibrosis, muscular dystrophy, etc., if there is no possibility of subsequent action? Progesterone antagonists and in vitro fertilization are examples of developments in reproductive research whose mode of action may cause them to be similarly threatened by the definition of conception as occurring at the time of fertilization. Governmental enforcement of particular theologic beliefs about conception and embryonic and fetal status will have a negative impact on the future of scientific advancement in reproductive medicine.

Legal first-trimester abortion has been one of the most scrutinized surgical procedures and has been demonstrated to be one of the safest.[3] Procedure-associated complications decreased as operator skill and experience grew.[4] If performance of abortion is not regularly included in obstetrics and gynecology training programs, it is likely that as experience decreases, complications will again rise, particularly for second-trimester procedures. Instead of training obstetrics and gynecology residents to be competent at this surgical procedure, we may soon have to teach them once again to diagnose and treat sepsis and other complications of an unsafe abortion.

On every previous occasion in which the Supreme Court has addressed the abortion issue, the Court has clearly stipulated that maternal health be the physician's paramount consideration and that her health cannot be sacrificed on behalf of the fetus.[5, 6] Indeed the trimester approach was based in part on the fact that legal abortion during the first trimester was safer than continuing the pregnancy to term. Today, for both first- and second-trimester legal abortion procedures, the risk of maternal death is significantly lower than that associated with childbirth.

While risks associated with both legal abortion and childbirth declined in the 1970s, the abortion-related risks declined much more steeply. From 1970 to 1982 maternal mortality associated with delivery declined 30% while abortion-associated mortality declined 89% and is approaching zero.[7]

The women most at risk of pregnancy-associated death or serious medical complications are the very women most likely to be affected by the prohibition on the use of public resources for abortion. The State of Missouri (and potentially others) is thus forcing poor women to endure significant risks and forcing physicians to collude in this.

Interestingly, restricted access to legal abortion for poor, high-risk women is likely to increase infant mortality rates. Access to legal abortion has been associated with a decline in infant mortality, attributed to the prevention of unwanted and high-risk pregnancies. Multivariate analysis of the impact of various health and social services on race-specific neonatal mortality revealed that access to abortion was the single most important factor in the reduction in the black neonatal mortality rate. In addition, the decline in the black neonatal mortality rate varied with financial access to this service.[8]

The effect of each of the Missouri restrictions will be to delay abortion, particularly for those women for whom financial barriers are significant. While the risks of serious complications of legal abortion remain less than for childbirth, they do rise with increasing gestational age.[7] Thus, by imposing cost and delay on women seeking abortion, such governmental regulations impose health risks. Lack of access to medical care always has the worst impact on those most in need of the service because they are already at higher health risk.

In the past decade, obstetricians have been involved in initiatives to decrease infant mortality in the United States, as well as maternal mortality internationally, by providing high-risk women with reproductive health care. Restrictions on access to abortion undermine these efforts to improve maternal and infant health.

Indeed restrictions on abortion subvert the physician's fundamental goal: to provide optimal care to the patient. Obstetricians working in public facilities, for example, will find themselves impeded in providing the best care to their patients if they can neither counsel patients about the option or advisability of termination of pregnancy nor ensure access.

In a recent review Annas et al.[9] pointed out that governmentally imposed constraints on communication between doctor and patient constitute a grave threat to the practice of medicine. Such regulation undermines a critical component of the doctor-patient relationship: the ability to freely and confidentially discuss options, absent outside intrusion. Indeed the legal doctrine of informed consent requires physicians to

share information with patients. The authors conclude that physicians and patients have a united interest in defending the right of privacy that protects their joint decision-making from governmental interference.

Historians inform us that one hundred years ago physicians worked to criminalize abortion partly in an effort to protect the health of women from unregulated, incompetent abortionists and partly to bolster their own professional identity and moral prestige.[10] Today these same goals demand that obstetricians work vigorously to ensure that safe abortion is part of a spectrum of reproductive health care that is accessible to all women in the United States.

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Chronic renal disease and pregnancy outcome

F. Gary Cunningham, MD, Susan M. Cox, MD, Timothy W. Harstad, MD, Ruble A. Mason, MT, and Jack A. Pritchard, MD
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During the 18-year period from 1971 through 1988, 37 women whose pregnancies were complicated by moderate or severe renal insufficiency were managed at Parkland Memorial Hospital. Common maternal complications included anemia, chronic hypertension, and preeclampsia. Perinatal complications included midpregnancy losses and low birth weight from preterm delivery, fetal growth retardation, or both. Despite the high incidence of maternal morbidity, 85% of pregnancies in the 26 women with moderate renal insufficiency resulted in a live-born infant; there was one stillbirth and no neonatal deaths. Of the 11 women with severe disease, seven were delivered of live-born infants after ≥26 weeks' gestation. Although six of these 37 women had worsening renal function during pregnancy, it seems unlikely that pregnancy per se caused this. More importantly, in four of these six women and in four others who had stable function throughout pregnancy, end-stage renal disease developed within a mean of 4 years after delivery. In 14 women blood volume was determined during pregnancy, and whereas those with moderate disease had normal volume expansion, women with severe disease had significantly attenuated expansion. Finally, serial creatinine clearances did not increase during pregnancy in half the women with moderate insufficiency and none with severe dysfunction. (Am J Obstet Gynecol 1990;163:453-9.)

Key words: Chronic renal insufficiency, pregnancy outcome

The effects of pregnancy on the natural course of chronic renal disease are not entirely clear. Whereas mildly impaired renal function usually does not worsen during pregnancy and generally is accompanied by uneventful pregnancy outcomes,[1] women with more seriously impaired renal function appear to do less well. For example, Hou and colleagues[2] described 23 women with moderate renal insufficiency, defined by a serum creatinine of ≥1.4 mg/dl, and approximately one third of these had worsening renal function during pregnancy. Other complications including hypertension and superimposed preeclampsia also were frequent. Although 92% of these women had live-born infants, 60% of these were delivered preterm, and the neonatal mortality rate was 10%. In this and most other studies of pregnant women, the degree of renal impairment was only mild. Pregnancy outcomes with more severe renal disease are less well defined but generally are assumed to be worse, and our purpose now is to describe our experiences with pregnancy complicated by moderate and severe renal insufficiency. In some of these women, blood volume was determined with erythrocytes labeled with chromium 51 and the magnitude of pregnancy-induced hypervolemia was correlated with the degree of renal insufficiency. Finally, whereas normal augmentation of pregnancy-induced glomerular filtration has been observed in women with mild renal disease, the response of those with more severe disease is unknown. We now report our observations in women with moderate or severe renal insufficiency.

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Material and methods

Patients. During the 18-year period from 1971 through 1988, 37 women with chronic renal insufficiency were followed up prospectively during pregnancy by at least one senior investigator (F. G. C. or J. A. P.). Creatinine in serum and urine was measured by the Jaffe method, which has an accuracy at 2 mg/dl and 5 mg/dl of 2.05 ± 0.13 and 4.98 ± 0.2, respectively.[3] The criteria of Davison and Lindheimer[4] were used to categorize the intensity of renal impairment;

Table I. Maternal findings and complications in 37 pregnancies complicated by chronic renal insufficiency

	Moderate insufficiency (%)	*Severe insufficiency (%)*
Total pregnancies	26	11
Serum creatinine (mean ± SEM)	1.7 ± 0.2 mg/ml	4.8 ± 0.7 mg/dl
Creatinine clearance (mean ± SEM)	43 ml/min ± 3.9	18 ml/min ± 3.1
Hematocrit (mean ± SEM)	28.0 ± 1.2	22.4 ± 1.5
Anemia (hematocrit < 30)	19 (73)	11 (100)
Chronic hypertension	16 (62)	9 (82)
Preeclampsia	15 (58)	7 (64)
Deterioration of renal function	5 (19)	1 (10)*

*Two others were first seen at midpregnancy with end-stage renal disease.

Table II. Long-term follow-up in six women with chronic renal insufficiency whose renal function worsened during pregnancy

		Pregnancy course			*Post partum*	
		Serum creatinine (mg/dl)	*Serum creatinine (μmol/L)*			
Patient no.	*Renal disease*	*Early*	*Late*	*Complication*	*Infant*	*Follow-up*
1	Diabetic nephropathy	1.4	3.8	Nephrotic syndrome, chronic hypertension given therapy	Term, 3460 gm	3 1/2 years; hypertensive; end-stage renal disease at 36 months, congestive heart failure, dialysis
2	Renal calculi; history of nephrolithotomy and nephrostomy	1.6	4.3	Pyelonephritis, obstruction required a stent	Preterm, 2406 gm	2 months, normotensive, serum creatinine 2.3 mg/dl
3	Systemic lupus erythematosus	1.9	4.8	Chronic hypertension given therapy; pregnancy-aggravated hypertension	Preterm growth-retarded 900 gm	1 year; hypertensive; end-stage renal disease and dialysis
4	Chronic pyelonephritis; meningomyelocele with reflux, Bricker pouch and cystectomy	3.8	6.6	Pregnancy-induced hypertension	Preterm, growth-retarded 1060 gm	4 years; hypertensive; end-stage renal disease at 24 months, dialysis
5	Adult polycystic kidney	1.8	3.5	Pregnancy-induced hypertension	Preterm, growth-retarded 760 gm; neonatal death	6 years, hypertensive; end-stage renal disease at 60 months, dialysis
6	Chronic pyelonephritis	1.4	3.8	Acute pylonephritis	Preterm, 2500 gm	15 years; mild hypertension serum creatinine 1.5 mg/dl

moderate insufficiency was defined by a serum creatinine concentration of 1.4 to 2.5 mg/dl, whereas severe impairment was defined by concentrations >2.5 mg/dl.

Definitions. Chronic hypertension was diagnosed if the diastolic blood pressure exceeded 90 mm Hg before pregnancy or before 20 weeks' gestation. In women with chronic hypertension, superimposed preeclampsia was defined as an increase in blood pressure along with development of proteinuria or significantly increased existing proteinuria. Anemia was defined by a hematocrit <30%. Arbitrarily, we considered worsening renal function to be significant in women whose serum creatinine levels increased by 50% during pregnancy. First-trimester abortions were excluded from analysis. Previability was defined as spontaneous or induced delivery before 26 weeks' gestation. Other outcomes assessed included perinatal death, fetal growth retardation defined by birth weight <10th percentile for gestational age, and preterm delivery defined as before 37 completed weeks' gestation. Mean serum creatinine values for each woman were plotted as a function of birth weight and linear regression was used to analyze this relationship. The paired Student *t* test[5] was used to compare creatinine clearances determined from 24-hour urine collections obtained in late pregnancy with those performed when the women were not pregnant.

Blood volumes and creatinine clearances. As part

Table III. Fetal outcome in 37 pregnancies complicated by chronic renal insufficiency

	Moderate insufficiency		*Severe insufficiency*	
	No.	*%*	*No.*	*%*
Total pregnancies	26	—	11	—
Midtrimester abortion (previable)				
Elective	0	0	2	18
Spontaneous	2	8	2	18
Live-born infants	23	88	7	64
Term	16	70	1	14
Preterm (<37 wk)	7	30	6	86
Fetal growth retardation	8	35	3	43
Stillborn*	1	4	0	0
Live-born birth weight (mean) (gm)	2500	—	1520	—

Fetal death after 26 weeks' gestation.

Table IV. Maternal and fetal outcomes in pregnancies complicated by chronic renal insufficiency and chronic hypertension

	Moderate disease		*Severe disease*	
	No.	*%*	*No.*	*%*
Pregnancies	14		7	
Worsening renal function	4	29	1	14
Superimposed preeclampsia	11	79	6	86
Preterm delivery	6	43	6	86
Fetal growth retardation	5	36	3	43
Perinatal mortality	1	7	0	0

of another investigation, we used the patients' erythrocytes labeled with chromium 51 to determine red cell mass and apparent blood volume in 14 of these women. Blood volume determinations were performed as previously described.[9] Informed consent was obtained, although these studies were conducted at a time before the general implementation of severe restrictions on the use of small amounts of radioisotopes in studies during pregnancy.[6] About 20 to 25 μCi were used for each determination, and the total maternal body dose was calculated to be approximately 6×10^{-3} cGy.[7] In women in whom preeclampsia developed, blood volume determinations made before the disease was clinically apparent were used for analysis. In 10 women, the blood volume was determined again when they were nonpregnant, and in four women calculated nonpregnant values were used for comparative purposes. From prior observations in normal nonpregnant women[8, 9] we determined that the blood volume was predictable within 10% of the radiochromium method by the following formula:

$$\frac{[\text{Weight in pounds} \times 25] + [\text{Height in inches} \times 50]}{2}$$

In all 14 of these women, plasma was obtained along with timed urine collections at least once during late pregnancy for determination of creatinine clearance by standard methods. In most women, serial clearances were determined, and in 12, creatinine clearance was again determined at least 6 weeks post partum.

Results

Maternal outcomes in the 37 women with moderate and severe chronic renal insufficiency are summarized separately in Table I. In the 26 women with moderate disease, serum creatinine averaged 1.7 mg/dl (range, 1.4 to 2.5 mg/dl) and five (19%) subsequently had a ≥50% increase in creatinine concentration during pregnancy. Of these 26 women, anemia was identified in 19 (73%) and 16 (62%) had chronic hypertension that was further complicated by superimposed preeclampsia in 80% of those whose pregnancy progressed beyond 26 weeks. By contrast, preeclampsia developed in one third of the women without chronic hypertension.

Also shown in Table I are the outcomes in 11 women with severe renal insufficiency whose creatinine levels averaged 4.8 mg/dl (range, 2.6 to 9.4 mg/dl). Although only one of these women demonstrated a

Table V. Mean blood volumes in pregnant women with chronic renal insufficiency compared with normally pregnant women

Category	No.	Nonpregnant volume (ml)	Late pregnancy volume		
			Volume (ml)	Range (ml)	%
Normal pregnancy	50*	3250	4820	3900-6500	+48
Chronic renal disease	14	3080	4450	2340-6820	+45
Normotensive prepregnant					
Normotensive	4	3220	4730	4260-5210	+47
Preeclampsia	1	2340	3780		+61
Hypertensive prepregnant					
No preeclampsia	5	2960	4170	3690-4560	+41
Preeclampsia	4	3270	4600	3180-6820	+41

*Data from Pritchard.[8]

significant increase in serum creatinine during pregnancy, two women were first seen at 18 and 20 weeks' gestation with end-stage renal failure and serum creatinine concentrations of 8.1 and 9.4 mg/dl, respectively. All women with severe disease had anemia, and chronic hypertension (80%) and preeclampsia (65%) also were frequent complications.

Further clinical details from the six women who were identified to have a ≥50% increase in serum creatinine concentration (mean 2.4 mg/dl; range, 1.9 to 3.0 mg/dl) are given in Table II. Five of these women were chronically hypertensive. These women were followed up for a mean of 5 years after delivery and four required dialysis 30 months on average after delivery. Long-term follow-up was available for only seven women whose renal function remained unchanged during pregnancy. They were followed up for a mean of 44 months and six had deterioration of renal function with four requiring dialysis by a mean interval of 39 months.

Fetal outcomes for these 37 pregnancies are summarized in Table III. Of the 26 women with moderate disease, there were two midtrimester losses before viability. Another 760 gm fetus died at 30 weeks; the mother had chronic hypertension and her serum creatinine level increased by >50% during pregnancy. There were no neonatal deaths in this group. In four of the 11 pregnancies complicated by severe disease, there was one midtrimester loss before viability. Two of these were induced abortions in women who required hemodialysis for end-stage renal disease, one pregnancy terminated spontaneously in a woman whose serum creatinine level was 5.7 mg/dl, and the fourth woman underwent abortion because of severe preeclampsia at 20 weeks' gestation. There were no perinatal deaths after 26 weeks' gestation in this group. As shown in Table III, compared with women with severe disease, those with moderate disease were more likely to be delivered of live births (88% versus 64%) and they had a lower incidence of fetal growth retardation (35% versus 43%) and preterm delivery (30% versus 86%).

Perinatal outcomes were analyzed separately for the 21 women with chronic hypertension. As shown in Table IV, fetal growth retardation and preterm delivery were identified more commonly in chronically hypertensive women with severe renal insufficiency. To determine whether birth weight was related to the degree of renal dysfunction, birth weights of the 29 live-born infants were plotted against maternal mean serum creatinine concentrations. As shown in Fig. 1, birth weight decreased significantly as creatinine concentration increased ($p < 0.001$).

The mean serum creatinine concentration of the 14 women who had blood volume determinations during pregnancy was 2.4 mg/dl and ranged from 1.4 to 5.5 mg/dl. Ten of these had moderate and four had severe disease. Nine women (64%) were known to have chronic hypertension before pregnancy, and superimposed preeclampsia developed in four of them. In the five women who were normotensive before pregnancy, preeclampsia developed in one. Mean blood volume determinations for these women are summarized in Table V, and are compared with volumes measured in normally pregnant women.[8, 9] As a group, pregnancy-induced hypervolemia developed in these women comparable to that of normal women. When the nine women with antecedent chronic hypertension were analyzed further, a normal volume expansion again was established.

To determine whether the degree of blood volume expansion correlated with the severity of renal impairment, the mean volumes for women with moderate and severe disease were compared. Whereas hypervolemia developed in the 10 women with moderate renal dysfunction similar to that of normally pregnant women, the four women with severe disease had significantly attenuated volume expansion. These latter four women had chronic hypertension and superimposed preeclampsia developed in two of them. As shown in Fig. 2, there was a significant inverse relationship between the incremental increase in blood volume plotted as a function of serum creatinine.

Blood volume measurements during pregnancy and remote from delivery in 10 women enabled us to quantify red cell mass expansion, which we found to be related inversely and significantly to serum creatinine. Erythrocyte mass expanded a mean of 26% in women with renal insufficiency, compared with 32% for normally pregnant women.[8, 9] Whereas this difference was not significant ($p = 0.13$), women with moderate renal insufficiency had significantly greater erythrocyte mass expansion compared with those with severe disease (26% versus 16%, $p = 0.04$). Because most of these women with renal disease already were anemic when nonpregnant (mean hematocrit, 31%), anemia was intensified during pregnancy because of disparately increased plasma volume compared with red cell mass. During late pregnancy their mean hematocrit was 27%, and in only three of the 14 was it ≥30%.

Creatinine clearance was determined in these same 14 women during pregnancy and again >6 weeks post partum. The late pregnancy mean clearance of 49 ml/min (range, 22 to 78 ml/min) was not significantly different from the nonpregnant mean of 52 ml/min (range, 16 to 77 ml/min). To determine whether changes in the glomerular filtration rate were related to blood volume expansion, we compared clearances that were determined in 12 of these women during pregnancy with clearances obtained again post partum. In eight women with moderate renal insufficiency, creatinine clearance increased by a mean of 23% at a time when blood volume expansion averaged 50% (range, 40% to 70%). In four of these eight women, there was no change in clearance despite pregnancy-induced hypervolemia that averaged 50%; however, in the other four clearance substantively increased. In the four women with severe renal impairment who were studied, creatinine clearance was unchanged despite blood volume expansion that averaged 23% (range, 13% to 33%).

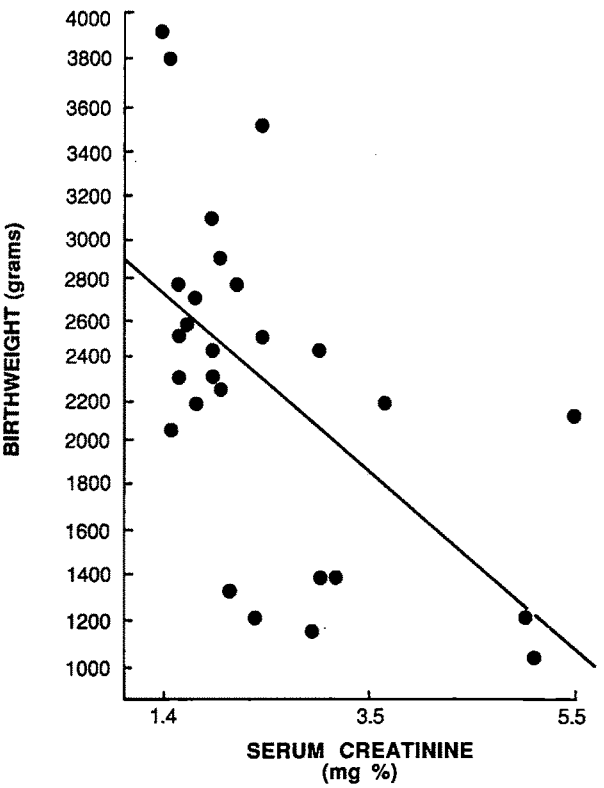


Fig. 1. Comparison of birth weight of 29 live-born infants with maternal serum creatinine concentration (Spearman correlation coefficient = −0.6252; $p = 0.001$).

Comment

Pregnancy in these women with moderate and severe chronic renal insufficiency commonly was complicated by chronic hypertension, preeclampsia, and anemia. Hypertension antedating pregnancy was identified in 68% of these 37 women, and others have reported incidences that range from 23% to 63% in women with mild to moderate disease.[2, 10, 11] Although it is sometimes difficult to identify preeclampsia accurately in women with chronic renal dysfunction, we made this diagnosis clinically in nearly 60%, and found it to be a major source of morbidity, particularly with regard to preterm birth. An important observation was that superimposed preeclampsia developed in 80% of women with chronic hypertension.

It has been reported that 8% to 50% of women with moderate renal insufficiency experience a decline in renal function during pregnancy.[2, 10-13] We documented significant worsening renal function in six women (16%), and perhaps unexpectedly, only one of these had severe dysfunction initially. We followed up these six women for a mean of 5 years; five continued to have worsening renal function and in four of these, dialysis became necessary for end-stage renal disease. It is important that poorly controlled chronic hypertension was implicated frequently in deterioration of renal function. Although the duration of our prepregnancy observation was inadequate to ascertain whether pregnancy-related events actually accelerated renal failure, this did not appear to be the case. Specifically, there were another six women who had stable renal function throughout pregnancy, but in whom deteriorating renal function later developed, and four of these ultimately required dialysis. In both groups of women (i.e., those with and without declining renal function during pregnancy) the mean interval from delivery-to-dialysis was similar (30 versus 39 months). Although some have suggested that women with lupus nephropathy, membranoproliferative glomerulonephritis, and immunoglobulin A and reflux nephropathy are more vulnerable to increasing renal damage during pregnancy,[14] we could not address this because most women now reported had not undergone renal biopsy sampling.

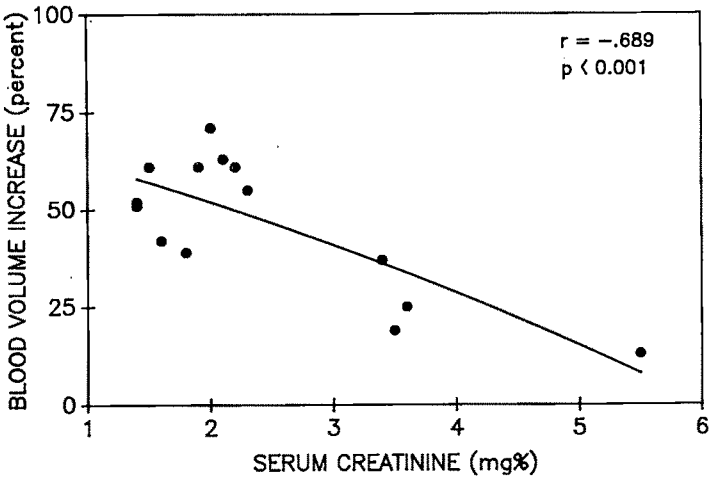


Fig. 2. Blood volume expansion during pregnancy plotted as function of serum creatinine concentration.

The causes of renal dysfunction, however, were known for the six women who had worsening function (Table II), and three of these are from these above-cited categories.

Although maternal complications were common in women now reported, adverse perinatal outcome was not prohibitive. For example, 80% of pregnancies resulted in live-born infants. Six pregnancies either aborted spontaneously or were electively terminated before 26 weeks' gestation. Loss before 26 weeks' gestation was more common in women with severe dysfunction, and two pregnancies were terminated surgically before dialysis in women with end-stage disease. For all women, perinatal mortality was limited to one third-trimester fetal death. Preterm delivery complicated 13 of 32 pregnancies (40%) that reached 26 weeks' gestation, and the mean birth weights in the moderate and severe renal disease groups were 2500 and 1520 gm, respectively. As shown in Fig. 1, birth weight correlated inversely with serum creatinine concentration; however, it was difficult to separate this relationship from chronic hypertension. In women with moderate insufficiency further complicated by chronic hypertension, preterm birth (43%) was more frequent than in normotensive women (10%). Superimposed preeclampsia developed in 80% of chronically hypertensive women and this also was associated with an even higher incidence of preterm birth (57%). It is important that superimposed preeclampsia not only developed earlier in pregnancy, but it tended to be more severe than in women who have normal renal function. Others have reported the incidence of preterm birth in women with chronic renal disease to be about 60%.[2, 10] Finally, hypertension was a common cofactor (73%) in women with fetal growth retardation, and indeed, 40% of infants of chronically hypertensive women were small for gestational age. The overall incidence of perinatal loss in women now reported was 3.2%, which compares favorably with reported figures for women with mild disease that range from 9% to 18%.[10, 12]

These findings confirm those of others that nonpregnant women with moderate to severe renal insufficiency have blood volumes comparable with those of women without renal disease.[15-17] Our observations are remarkably similar to those reported by Eisenberg[15] who used radiochromium-labeled erythrocytes to estimate blood volume in eight men with the nephrotic syndrome whose serum creatinine values ranged from 1.5 to 3.6 mg/dl. It is important that we found also that women with chronic renal insufficiency usually have normal blood volume expansion in response to pregnancy. This increase, which averages about 50% in normal women,[8] was almost identical in women with moderate disease; however, it was attenuated significantly in those with severe disease. Specifically, whereas pregnancy-induced hypervolemia averaged 51% in women with moderate renal impairment, it was only 23% in those with severe disease. As shown in Fig. 2, the magnitude of volume expansion was inversely proportional to serum creatinine.

An intriguing finding was that most of these women responded to pregnancy with increased erythropoiesis. Although most were anemic when not pregnant, mean red cell mass increased 23% during pregnancy. As with blood volume expansion, this corresponded to the degree of renal impairment, and erythrocyte mass expansion related inversely to the serum creatinine. Because red cell mass expansion was less pronounced than

blood volume expansion, preexisting anemia usually was intensified. Pregnancy-induced erythropoiesis presumably is related to increased erythropoietin production,[18, 19] but this has not been fully evaluated and we can only speculate that these women with chronic renal insufficiency had augmented erythropoietin secretion.

Although Katz[11] has reported that the glomerular filtration rate and effective renal plasma flow increased incrementally in pregnancy complicated by mild renal disease, and similar to normal pregnancy, only one of 33 women that he described had a serum creatinine level >1.4 mg/dl. It is important that hypertension may cause further nephron damage, ultimately leading to further glomerular injury.[20] From the current study it is apparent that augmentation of glomerular filtration in these women with moderate to severe renal insufficiency was not solely a result of pregnancy-induced hypervolemia. When paired blood volume and creatinine clearance determinations during pregnancy and again post partum were compared, despite an average volume expansion of 50% in eight women with moderate dysfunction, the glomerular filtration rate increased by a mean of only 23%. Indeed four of these eight women had no increase in their glomerular filtration rate. None of the four women with severe renal impairment had augmented glomerular filtration during pregnancy. These latter findings are supportive of the theory that increased glomerular filtration is mediated at least partially by pregnancy-induced vasodilation.[21-22] In this scheme, because severe renal insufficiency is characterized by maximal vasodilation, augmentation of renal function as a result of pregnancy is not possible. It is important that it has been shown that severe hypertension may be harmful to these already-damaged nephrons, leading to further glomerular injury.

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Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986

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Preeclampsia and eclampsia continue to be among the leading causes of maternal death. However, national estimates of the occurrence of these conditions have not been available. To derive national rates of preeclampsia and eclampsia and to characterize the women at highest risk of the development of these conditions, we analyzed data from the National Hospital Discharge Survey for the years 1979 through 1986. We found that 26 per 1000 births during this period were complicated by preeclampsia and 0.56 per 1000 births were complicated by eclampsia. The rate of mild or unspecified preeclampsia remained constant over the study period. In contrast, the rate of severe preeclampsia increased sharply and the rate of eclampsia declined by 36%. Maternal age <20 years old was the strongest risk factor for both preeclampsia and eclampsia. These data indicate a need for improved prenatal care among teenagers. (AM J OBSTET GYNECOL 1990;163:460-5.)

Key words: Preeclampsia, eclampsia, pregnancy-induced hypertension, maternal morbidity

Preeclampsia and eclampsia continue to be important public health problems in the United States. In recent studies, these conditions were shown to be the second leading cause of maternal death[1, 2] and were associated with increased risk of abruptio placentae,[3] disseminated intravascular coagulation, acute renal failure, and cerebral hemorrhage.[4] In addition, preeclampsia and eclampsia reduce uteroplacental perfusion, which places the fetus at high risk of intrauterine growth retardation, preterm birth, and perinatal mortality.[4, 5] However, proper obstetric care and antenatal fetal assessment can minimize the maternal and fetal morbidity and mortality from these conditions.[4]

Although preeclampsia and eclampsia have been studied extensively worldwide, their cause remains unknown. Hypotheses have focused on numerous etiologic factors including the role of endogenous hormones,[6] nutrition,[7, 8] immunologic factors,[9] and family history of these conditions.[10] However, few well controlled epidemiologic studies of risk factors for preeclampsia and eclampsia have been conducted.

Most estimates of the incidence of preeclampsia and of eclampsia in the United States have been made on the basis of nonrepresentative clinical series or multicenter studies. The incidence of these conditions is generally given as 5% to 7% of all deliveries.[4] To estimate the incidence of preeclampsia and eclampsia on a national level, we analyzed data from a representative sample of hospital discharge records nationwide. In addition, we evaluated demographic risk factors for preeclampsia and eclampsia and trends in occurrence over an 8-year period from 1979 through 1986.

Material and methods

The Committee on Terminology of the American College of Obstetricians and Gynecologists defines preeclampsia as hypertension induced by pregnancy after 20 weeks' gestation concurrent with proteinuria or edema or both.[11] Hypertension is defined as a diastolic pressure of at least 90 mm Hg, a systolic pressure of at least 140 mm Hg, or a rise from baseline of 15 mm Hg diastolic pressure or 30 mm Hg systolic pressure. The elevated blood pressure readings must occur on at least two occasions at least 6 hours apart. Eclampsia, a severe complication of preeclampsia, is defined as the occurrence of convulsions unrelated to coincidental neurologic disease in a woman with preeclampsia.

Data for this study were obtained from the National Hospital Discharge Survey, conducted by the National Center for Health Statistics. Since 1965 this survey has obtained a nationally representative sample of discharge records from nonfederal short-stay hospitals in the United States.[12] Each year approximately 200,000 patient records are abstracted from approximately 400 hospitals and weighted to represent all such hospital discharges nationwide.[12] Up to seven discharge diagnoses and four operative procedures are abstracted

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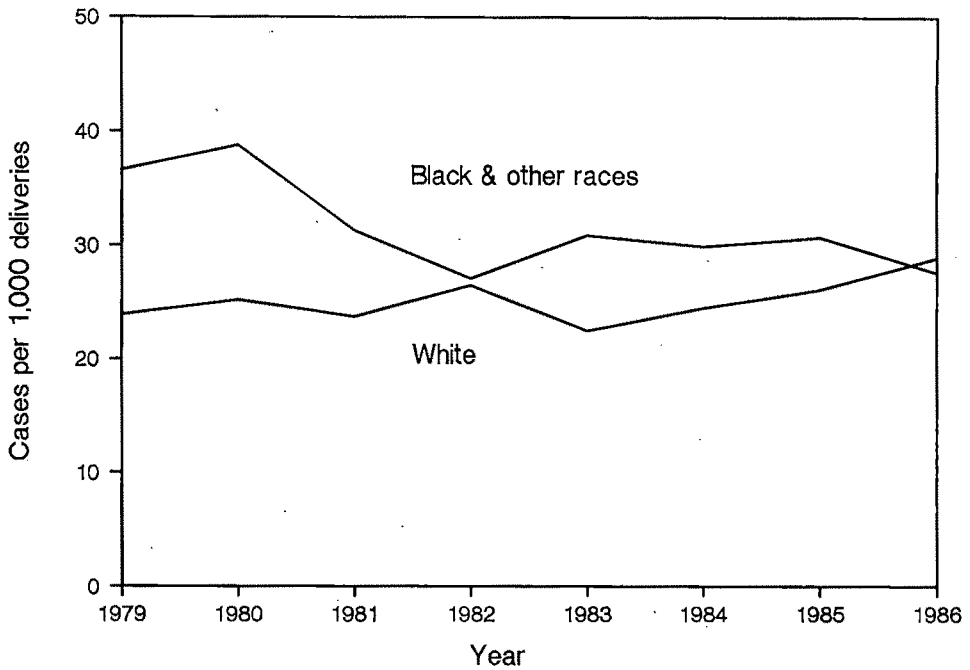


Fig. 1. Age-adjusted rate of preeclampsia by race, National Hospital Discharge Survey 1979 to 1986.

Table I. Number of cases and incidence rates per 1000 deliveries for women with preeclampsia, by severity, National Hospital Discharge Survey 1979 to 1986

	Year								
Preeclampsia	*1979*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1979-1986*
Mild, unspecified									
No. of cases	84,800	96,500	89,700	92,200	84,900	83,800	84,100	87,000	87,900
Rate	23.2	25.6	22.9	23.4	21.4	21.8	21.8	23.1	22.9
Severe									
No. of cases	8,600	9,400	11,500	10,400	10,400	10,800	18,000	19,700	12,300
Rate	2.4	2.5	2.9	2.6	2.6	2.8	4.7	5.2	3.2
Total									
No. of cases	93,400	105,900	101,200	102,600	95,300	94,600	102,100	106,700	100,200
Rate	25.6	28.1	25.9	26.0	24.0	24.6	26.5	28.4	26.1

from the face sheet of each hospital record sampled and coded according to the *International Classification of Diseases,* 9th Revision, Clinical Modification (ICD-9-CM). Available data items include date of birth, sex, race, marital status, expected source of payment for hospitalization, and geographic region of residence in the United States.

The study population consisted of all sampled women who were delivered of a stillborn or live-born infant in the hospital during 1979 through 1986. Incidence rates were calculated per 1000 deliveries for mild or unspecified preeclampsia (code 642.4), severe preeclampsia (code 642.5), and eclampsia (code 642.6). We do not discuss preeclampsia and eclampsia superimposed on preexisting hypertension because our analyses showed that demographic risk factors for these conditions are more like those for chronic hypertension than those for de novo hypertension during pregnancy. For some analyses, when severity of preeclampsia was not specified, categories were combined. Rate ratios were also calculated to evaluate the risk of preeclampsia and eclampsia associated with several demographic variables. To evaluate the trend in the rate of eclampsia during the study period, we calculated average annual age-adjusted rates for two time periods: 1979 through 1982 and 1983 through 1986.

We used direct standardization to adjust incidence rates for the effects of age and race.[13] The standard

Table II. Number of cases (in thousands), adjusted incidence rates per 1000 deliveries, and rate ratios for women with preeclampsia, by selected demographic characteristics, National Hospital Discharge Survey 1979 to 1986

Demographic variable	Racial group							
	White				Black and other minorities			
	No. cases	Rate†	Rate ratio†	(95% CI)	No. cases	Rate†	Rate ratio†	(95% CI)
Age group (yr)								
<15	1.8	§	§	—	4.6	§	§	—
15-17	43.7	50.9	2.6	(2.1-3.1)	29.7	56.9	2.4	(1.7-3.1)
18-19	58.5	34.5	1.8	(1.4-2.1)	34.8	48.4	2.0	(1.5-2.5)
20-24	179.9	27.3	1.4	(1.2-1.6)	53.8	27.3	1.1	(0.9-1.4)
25-29	137.5	19.6	1.0	(0.8-1.2)	39.9	27.0	1.1	(0.8-1.4)
30-34	74.8	19.6	1.0	Referent	18.7	24.2	1.0	Referent
35+	27.4	23.0	1.2	(0.9-1.4)	12.5	40.1	1.7	(1.2-2.2)
Marital status								
Married	403.4	24.3	1.0	Referent	70.1	28.2	1.0	Referent
Unmarried	86.7	31.0	1.3	(1.1-1.5)	109.7	35.4	1.3	(1.0-1.5)
Region								
Northeast	77.7	20.0	1.0	Referent	37.7	30.0	1.0	Referent
North central	125.1	22.4	1.1	(0.9-1.3)	38.5	33.5	1.1	(0.8-1.5)
South	206.0	28.7	1.4	(1.1-1.7)	100.9	31.4	1.0	(0.8-1.3)
West	118.1	31.4	1.6	(1.1-2.1)	19.2	27.8	0.9	(0.6-1.2)

CI, Confidence interval.
*Includes women whose race was not known.
†Adjusted for age.
‡Adjusted for age; marital status estimates adjusted for age and race.
§Estimates made on basis of fewer than 5000 cases; not reliable.

Table III. Number of cases, adjused incidence rates per 1000 deliveries, and rate ratios for women with eclampsia, by selected demographic characteristics, National Hospital Discharge Survey 1979 to 1986

Demographic variable	No. cases	Rate	Rate ratio	(95% CI)
Age group (yr)				
<20	7,800	1.82	4.9	(2.5-7.4)
20+	9,211	0.37	1.0	Referent
Race*				
White	10,300	0.51	1.0	Referent
Black and other	6,000	0.83	1.6	(0.8-2.5)
Marital status†				
Married	8,800	0.50	1.0	Referent
Unmarried	6,700	0.60	1.2	(0.1-2.3)

CI, Confidence interval.
*Adjusted for age.
†Adjusted for age and race.

population consisted of all women in the survey who were delivered of a stillborn or live-born infant during the 8-year study period.

With the use of the computer program SESUDAAN (Research Triangle Institute, Research Triangle Park, N.C.), we calculated crude and adjusted incidence rates and their corresponding SE, taking into account the complex multistage sampling design of the National Hospital Discharge Survey.[14] For computing SE, we used a first-order Taylor series linearization.[15] We also applied Taylor series expansion to rate ratios and calculated 95% confidence intervals with SESUDAAN to estimate the variance and covariance terms. Weighted linear regression was used to test for linear trend in rates of preeclampsia over the 8-year period.[16] Rates and rate ratios are given only for weighted numerators of ≥5000 discharges because estimates of <5000 are considered unreliable.[12]

After stratification by type of delivery, we also estimated the mean length of hospital stay for women whose pregnancies were normotensive and for those whose pregnancies were complicated by preeclampsia or eclampsia.

Results

An average of 100,200 deliveries were complicated by preeclampsia during each year of the 8-year study period (Table I). The average annual incidence rate was 26 cases per 1000 deliveries. The rate of preeclampsia fluctuated only slightly over the study period. Whereas the rate of mild or unspecified preeclampsia decreased slightly during the study period, the rate of severe preeclampsia increased sharply from 2.9 cases per 1000 deliveries in 1984 to 5.2 cases per 1000 deliveries in 1986 (test for linear trend, $p < 0.01$). This increase was observed among women of both racial groups (data not shown).

Fig. 1 shows the trend in age-adjusted rates of preeclampsia by racial group over the study period. The

Racial group			
All races*			
No. cases	Rate‡	Rate ratio‡	(95% CI)
6.9	55.7	2.8	(1.6-4.0)
80.5	51.9	2.6	(2.1-3.1)
100.9	36.7	1.9	(1.6-2.1)
262.2	27.2	1.4	(1.2-1.6)
199.9	21.1	1.1	(0.9-1.2)
101.5	19.8	1.0	Referent
43.1	25.4	1.3	(1.0-1.5)
527.6	24.9	1.0	Referent
214.5	32.1	1.3	(1.2-1.5)
125.1	22.9	1.0	Referent
185.7	24.8	1.1	(0.8-1.3)
318.9	28.1	1.2	(1.0-1.5)
171.8	27.3	1.2	(1.0-1.4)

rate for women of black and other minority races appears to be declining (test for linear trend, $p = 0.06$), whereas the rate for white women has been relatively stable (test for linear trend, $p = 0.27$). Between 1979 and 1985 the incidence of preeclampsia among women of black and other minority races was higher than that among white women; however, rates for the two racial groups crossed over in 1986 when the rate was 28.3 cases per 1000 deliveries for white women and 27.6 cases per 1000 deliveries for women of black and other minority races. The greatest racial disparity in the rate of preeclampsia occurred in 1979 and 1980; however, these differences were of borderline statistical significance ($0.10 > p > 0.05$).

Table II shows by race, the number of cases, rates, and rate ratios for preeclampsia associated with selected demographic characteristics. For the study period, the risk of preeclampsia was most strongly associated with maternal age in a reverse J-shaped curve. Women under the age of 15 years had a 2.8-fold higher risk of the development of preeclampsia than did women ages 30 to 34 years old. Risk decreased with age until age 35 years when it increased significantly for women of black and other minority races.

Stratification by marital status showed that single women were at significantly greater risk of the development of preeclampsia (rate ratio = 1.29) than were married women. When rate ratios were examined by geographic region, we found that white women who resided in the South and West had a significantly higher rate of preeclampsia than did white women who resided in the Northeast. In contrast, little regional variation in the risk of preeclampsia was noted among women of black and other minority races. Analysis by primary source of expected payment for hospitalization showed no significant difference in the risk of preeclampsia among women on Medicaid than among women who had private health insurance (data not shown).

Eclampsia occurred much less frequently than did preeclampsia. An average of 2000 deliveries were complicated by eclampsia annually during the study period, for an average annual rate of 0.56 cases per 1000 deliveries (data not shown). The rate decreased by 36% from 0.68 cases per 1000 deliveries for 1979 through 1982 to 0.43 cases per 1000 deliveries during 1983 through 1986.

We also calculated rates and rate ratios for the occurrence of eclampsia in different subgroups for the period 1979 through 1986 (Table III). Maternal age was most strongly associated with risk of eclampsia. Women under the age of 20 years had nearly a fivefold greater risk of the development of eclampsia than did women 20 years of age or older. Race and marital status were not significantly associated with risk of preeclampsia. Because of the low number of women with eclampsia, we were not able to evaluate variations in rates by region or by expected source of payment.

Mean length of stay in the hospital was determined for women who had preeclampsia or eclampsia and for those who gave birth but remained normotensive throughout pregnancy (Table IV). All estimates were stratified according to whether the birth was vaginal or by cesarean section. It was necessary to stratify by type of delivery because women with preeclampsia or eclampsia were 2.4 times more likely to have had a cesarean section (rate = 46.5%) than were normotensive women (rate = 19.1%).

The mean length of stay decreased over the 8-year study period for women in all categories. Among women who had a vaginal delivery, those with preeclampsia or eclampsia were hospitalized an average of 1.5 days longer than were normotensive women; among women who had a cesarean birth, those with preeclampsia or eclampsia were hospitalized an average of 1.8 days longer than were normotensive women.

Comment

Analysis of National Hospital Discharge Survey data indicates that preeclampsia complicated 26 per 1000 deliveries or 2.6% of all births from 1979 to 1986. This rate is lower than that reported by most hospital-based studies. The higher rates may be attributable to the many high-risk patients in referral hospitals. Because our rate was calculated by use of a representative sample of hospital discharge records from across the United States, it more accurately represents the rate for the total U.S. population. The rate of preeclampsia we found is similar to that reported by the National Natality Survey (Unpublished data) and two other clinic

Table IV. Mean length of hospital stay (days) among women with preeclampsia or eclampsia and among normotensive women, by type of birth, National Hospital Discharge Survey 1979 to 1986

	Year							
Type of birth	*1979*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*
Vaginal								
Normotensive	3.1	3.1	3.1	3.0	2.9	2.8	2.6	2.6
Preeclampsia or eclampsia	4.4	4.9	4.9	4.6	4.6	4.1	4.1	3.7
Cesarean								
Normotensive	6.3	6.2	6.2	5.8	5.7	5.5	5.1	4.9
Preeclampsia or eclampsia	8.7	8.7	8.2	7.0	7.6	7.0	6.9	6.1

and hospital-based studies[8, 17] but is lower than the rates of preeclampsia of 4.5% and 11.2% reported for whites and blacks, respectively, by the U.S. Collaborative Perinatal Study.[18]

Eclampsia complicated 0.56 per 1000 deliveries over the 8-year study period. Although this rate is lower than those reported by other hospital-based studies in the United States,[4] it is only slightly less than rates estimated by the U.S. Collaborative Perinatal Study for the years 1959 through 1965 (white women, 0.61 cases per 1000 deliveries; black women, 0.75 cases per 1000 deliveries).[18] In contrast, the eclampsia rate we found is two times higher than the rate of 0.27 per 1000 deliveries reported for the population of Sweden for 1976 through 1980.[19] The low rate of eclampsia in Sweden was attributed to the early and regular prenatal care received by the majority of Swedish women.

We found young maternal age to be the strongest risk factor for both preeclampsia and eclampsia; teenagers were at significantly higher risk than were women 25 to 34 years of age. This finding is consistent with the clinical observation that preeclampsia is primarily a condition of young primigravid women.[4] Our findings are also in accord with those of Zlatnik and Burmeister[8] who found that young maternal age was significantly associated with risk of preeclampsia, even after controlling for the effects of parity and ponderal index. However, other studies have reported that the rate of preeclampsia and eclampsia increased with maternal age, before and after controlling for parity.[18, 20, 21] Because we lacked data on parity we could not evaluate the independent effects of maternal age and parity. Additional studies are needed to clarify the role of parity and age on the risk of preeclampsia.

Race was not a significant risk factor for either preeclampsia or eclampsia. From 1979 to 1986 the rate of preeclampsia decreased among women of black and other minority races but varied little among white women. By 1986, rates for the two groups were virtually equivalent. We were unable to identify any subgroup of black and other minority women that could account for the decrease in rate over time; decreases were found for all geographic areas, payment categories, marital status groups, and age groups, except for women ages 20 to 24 years and 35 years or older. Several studies have reported higher rates of preeclampsia and eclampsia among black women than among white women in the United States.[17, 18] Black American women have a higher rate of chronic hypertension than that of white women; thus the higher rates of preeclampsia that we found for minority women early in the study period may have been biased by misclassification of chronic hypertension as preeclampsia.

Unmarried women had a significantly higher rate of preeclampsia than that of married women. However, most other studies have reported no difference in risk by marital status. Our finding may be a result of a higher proportion of primiparous women among the unmarried.

Although race was not a statistically significant risk factor for either preeclampsia or eclampsia, proportionately more women of black and other minority races were under 20 years old and unmarried at the time of childbirth than were white women. Thus the burden of illness from preeclampsia and eclampsia is greater among minority women.

Women whose hospital stays were financed by Medicaid were no more likely to have preeclampsia than were women who had private insurance. With the assumption that women who use Medicaid and women who have private insurance represent two distinct socioeconomic groups, we observed no difference in risk by socioeconomic status. This finding is consistent with that of a Scottish study in which the incidence of preeclampsia did not differ significantly among five social classes.[22]

Our finding of a significantly higher rate of preeclampsia among white women who resided in the South and West compared with those who resided in the Northeast is difficult to explain, particularly because there was little regional variation in the rate among black and other minority women. Nevertheless, these regional differences in the rate of preeclampsia among white women could reflect regional variation in diagnostic practice or true regional differences in the rate of this condition.

We found that the rate of eclampsia decreased over the 8-year study period, whereas the rate of severe preeclampsia was relatively constant from 1979 to 1984 and then sharply increased. Although we cannot be sure of whether these trends are real, the increase in incidence of severe preeclampsia could be a consequence of changes in diagnosis of this condition. Diagnostic-related groups instituted in 1984 may have prompted physicians to provide more accurate reporting of severe preeclampsia or to overdiagnose the condition. When the categories of preeclampsia were combined the rate of preeclampsia varied little over the 8-year study period, which suggests that perhaps more cases of mild or unspecified preeclampsia after 1984 were classified as severe. Because eclamptic convulsions are so dramatic, this diagnosis is rarely missed. Thus we believe that the decline in the rate of eclampsia reflects improved antenatal management of women with preeclampsia. However, the decline in the number of women with eclampsia is not sufficient to explain the increase in the rate of severe preeclampsia.

Women with preeclampsia or eclampsia stayed in the hospital substantially longer than did normotensive women, regardless of method of delivery. This finding has economic implications. Given the longer hospital stay and high rate of cesarean section among women with these conditions, an excess of 217,700 hospital days for delivery admissions in 1986 are attributable to preeclampsia and eclampsia.

Our analysis is limited by the lack of data on important variables such as parity, the inability to distinguish any racial or ethnic groups among women of minority races, and the lack of standardized definitions of preeclampsia among physicians. The Committee on Terminology's criteria[11] for preeclampsia is one of several used by researchers when studying this condition. For this reason, researchers agree that a standardized, international definiton of preeclampsia is necessary. Despite these limitations, we found the National Hospital Discharge Survey to be a good data source to describe the epidemiology of preeclampsia and eclampsia.

Our data indicate that eclampsia develops in approximately 2000 women per year, although most cases of eclampsia are considred preventable with good obstetric care. Teenagers are at highest risk of eclampsia and are also more likely than other women not to receive prenatal care.[23] However, for a given woman, whether eclampsia can be attributed to inadequate prenatal care remains unknown. Case reviews and epidemiologic studies of eclampsia should be undertaken to address this issue directly so that public health recommendations can be made. In addition, well designed epidemiologic studies are needed to determine risk factors for preeclampsia that will identify women at high risk of the development of this condition and lead to risk reduction strategies.

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Transvaginal ultrasonographic detection of congenital anomalies in the first trimester

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Transvaginal ultrasonography enables detailed visualization of the first-trimester pregnancy. Thirty-three structural anomalies have been diagnosed in the first trimester of pregnancy during a 2-year study period. An understanding of normal embryonic development is essential before attempting diagnosis in this gestational period. (AM J OBSTET GYNECOL 1990;163:466-76.)

Key words: Pregnancy, prenatal diagnosis, first trimester, transvaginal ultrasonography

The development of transvaginal ultrasonography enables earlier and more detailed examination of the first-trimester conceptus.[1-3] Enhanced visualization and an understanding of normal embryologic development as depicted by ultrasound may allow the detection of congenital anomalies in the first trimester. Early diagnosis alleviates the morbidity and expense associated with second-trimester abortion, as well as the anxiety engendered by waiting for testing at a later period. We present our experience with the antenatal detection of congenital anomalies in the first trimester and suggest some limitations of this practice.

Material and methods

During a 2-year study period ending February 1989, 805 ultrasonographic examinations were performed on 622 first-trimester fetuses at the Perinatal Unit of Yale University School of Medicine. Patients were referred as part of an ongoing evaluation of the efficacy of prenatal diagnosis in the first trimester. Criteria for entry into the study included a gestational age of 13 menstrual weeks or less with a live embryo at the time of the examination. Scans were repeated in gestations <10 weeks.

Ultrasonographic examinations were performed abdominally (General Electric 3000, Milwaukee; Corometrics Aloka 280 SL, Wallingford, Conn.) and transvaginally (Advanced Technology Laboratories UM-4, Bothell, Wash.). All sonograms were performed and videotapes subsequently reviewed by at least two of the authors. The assessment included a complete anatomic survey including evaluation of the ventral and dorsal wall, calvarium, face, extremities, placenta, and umbilical cord. Most patients underwent a complete anatomic survey at 16 to 18 weeks' gestation.

Gestational age was calculated from last menstrual period. If a discrepancy of greater than plus or minus 5 days was observed, the ultrasound assessment was used. In this study all gestational ages were expressed in menstrual weeks.

Structural anomalies were grouped by the most significant anatomic lesion. Embryos with isolated choroid plexus cysts were not included in this study.

In cases of pregnancy termination, gentle embryo extraction was performed. Pathologic examination was performed by a pathologist experienced in developmental embryology.

Results

Thirty-three embryos were identified as having structural anomalies in the 622 patients studied (0.5%). Table I lists the structural anomalies found at pathologic examination, ultrasound findings, gestational age at the time of diagnosis, and pregnancy outcome. The indications for referral of the fetuses with a detected anomaly were as follows: before chorionic villus sampling, 11; maternal diabetes, 2; history of an anomaly in a previous pregnancy, 2; pregnancy dating, 11; and a suspicious scan at another institution, 7 cases.

The outcome of each pregnancy was available in all cases in which an anomaly was suspected. Gestational ages at the time of diagnosis ranged from 8 to 13 weeks (mean, 11 weeks). Although not all fetuses that had a normal scan were reviewed, the referral population is localized to New Haven, where a missed anomaly is routinely reported by the community.

Four ventral wall defects were diagnosed, five neural tube defects, five urinary tract abnormalities, nineteen

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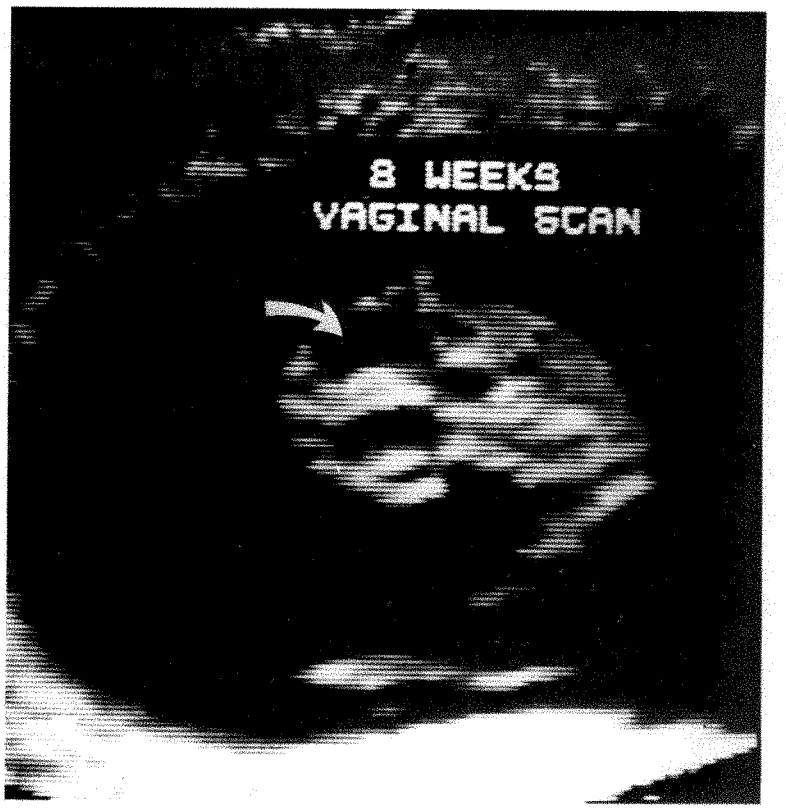


Fig. 1. Sagittal scan in a normal 8-week embryo demonstrating large sonolucent posterior fossa *(arrow)*. This should not be confused with Dandy-Walker malformation.

Table I. Structural anomalies diagnosed by major anatomic malformation and pregnancy outcome

Case No.	*Structural anomaly at ultrasonographic diagnosis*	*Gestation at diagnosis (wk)*	*Pathologic diagnosis*	*Pregnancy outcome*
1	Folding defect	12	Folding/ventral wall defect	TOP 12 wk
2	Acrania	12	Acrania	TOP 13 wk
3	Omphalocele, cystic hygroma, hydronephrosis	12	Same	TOP 13 wk
4	Polydactyly, cystic hygroma, low-set ears	11	Same	TOP 13 wk
5	Bladder outlet obstruction	13	Same	PG 18 wk
6	Bladder outlet obstruction	11	Same	TOP 13 wk
7	Acrania	11	Same	TOP 13 wk
8	Cord cyst	10	Resolved 15 wk	NSVD at term, resolved
9	Mono twins; 1 normal, 1 hypotelorism & exencephaly	13	Inadequate specimen	TOP 13 wk
10	Kyphoscolosis, encephalocele, gastroschisis	11	Same	TOP 12 wk
11	Cranial cyst	9	Macerated	Death 9 wk
12	Omphalocele, hydronephrosis, urachal cyst	12	Omphalocele, cloacal defect	NSVD, term
13	Cystic dysplastic kidneys	11	Same (ultrasonographic diagnosis)	NSVD, affected neonate
14	Macroyolk sac	8	Same	Death 9 wk
15-33	Cystic hygroma (n = 19) (isolated)	10-12	Same	NSVD resolved (n = 2); TOP and death (n = 19)

TOP, Termination of pregnancy; *PG,* prostaglandin abortion; *NSVD,* normal spontaneous vaginal delivery.

isolated cystic hygromas, and two anomalies of the cord or yolk sac were seen. In two cases there were more than one significant anomaly.

Of the 33 defects that were diagnosed, 23 patients had elective first-trimester abortions, four had spontaneous fetal deaths, one underwent a prostaglandin abortion in the second trimester, and five were delivered at term.

Pathologic confirmation of terminated specimens was accomplished in all but three cases. In cases 11 and 14, the nonviable embryos were macerated; however, embryoscopic verification[4] was possible in case 14. In case 10 the specimen was inadequate for pathologic examination as a result of the abortion procedure. There were three instances in which the lesion resolved: one large umbilical cord cyst and two cystic hygromas.

Comment

Prenatal diagnosis of congenital anomalies has advanced the practice of modern obstetrics. Diagnosis in the first trimester is advantageous because it lessens the anxiety and morbidity of second-trimester diagnosis and abortion.

Technical advances in ultrasonography and the advent of transvaginal ultrasonography now afford superior visualization of the embryo.[2, 3] Improved resolution, in conjunction with a growing interest in early diagnosis, which includes ultrasonography, chorionic villus sampling, and amniocentesis, will lead to a greater number of embryos undergoing an ultrasound examination. With a higher incidence of chromosomal abnormalities in the first trimester[5] and a known association of structural anomalies with aneuploidy, we expect that more anomalies will be identified in the first trimester as more scans are performed.

Green and Hobbins[1] and Timor-Tritsch et al.[3] have recently described the normal ultrasonographic appearance of the developing embryo throughout the first trimester. These data afford the background necessary for ultrasonography to be used for the detection of congenital anomalies. The series presented here and case reports in the literature illustrate the utility of ultrasonography in first-trimester diagnosis.

A review of developmental anatomy and diagnostic criteria and limitations for specific anomalies are discussed below by anatomic location.

Head and neck. The intracranial anatomy initially appears as a single ventricle with the rhombencephalon at 8 weeks. The large posterior position of the rhombencephalon (Fig. 1) should not be confused with a Dandy-Walker malformation. The falx cerebri can be seen dividing the midline with two prominent choroid plexuses at 9 weeks, whereas calcification of the calvarium and visualization of the cerebellum does not become apparent until the tenth week. The ventricles, with the prominent choroid plexus are seen filling the calvarium throughout the first trimester. A small amount of cortex can be seen at the periphery by the end of the twelfth week. Because the corpus collosum, which is superior to the third ventricle, does not fully develop until the second trimester, the third ventricle may be seen at a level higher than the thalamus (Fig. 2). The antenatal diagnosis of hydrocephaly without craniomegaly is not likely due to the large relative proportions of the lateral ventricles to the calvarium.

From the above observations of normal neuroanatomic development, it is clear that anencephaly (Fig. 3), exencephaly (Figs. 4 and 5), encephalocele and acrania cannot be diagnosed until after 10 weeks when the calvarium is calcified.[6] These conditions are illustrated in cases 2, 7, 9, and 10. Exencephaly was diagnosed by the presence of an irregular mass that represented disorganized neural and vascular tissue with the absence of a calvarium. Anencephaly, which is thought to be a progression from exencephaly through mechanical abrasion, might appear at a later gestation. In embryos with acrania, normal cerebral cortex is seen without a bony calvarium. The diagnosis of an encephalocele should be considered when a calcified cranium is seen with protruding neural tissue. Choroid plexus cysts appear as well-defined sonolucencies in the choroid plexus and are occasionally seen in the first trimester.[1] The significance of this finding is currently unclear.

Face. The mandible and maxilla are visualized at 10 weeks, well after the seventh week when there is complete fusion of the midline structures. There have been no reported cases in which the prenatal diagnosis of midline clefting has been made in the first trimester, although it should be possible. The external ears are seen at 8 weeks. Low-set ears were apparent in case 4 (Fig. 6), which was associated with multiple anomalies and trisomy 13. Case 9 demonstrates hypotelorism (Fig. 5) in a case with a neural tube defect. Recently we have examined a woman with class D diabetes whose embryo was scanned at 10.5 weeks, before long bone mineralization, and appeared normal. At 18 weeks the fetus was found to have micrognathia and mesomelic limb dysplasia.

Spine. The dorsal wall can be seen in the sixth week. Closure of the neural pore and calcification of the lamina of the spine do not occur until 6 and 10 weeks, respectively, at which time it is possible to diagnose some neural tube defects.[7] Kyphoscoliosis is demonstrated in case 9 by observing the misalignment of the lamina and spinal body.

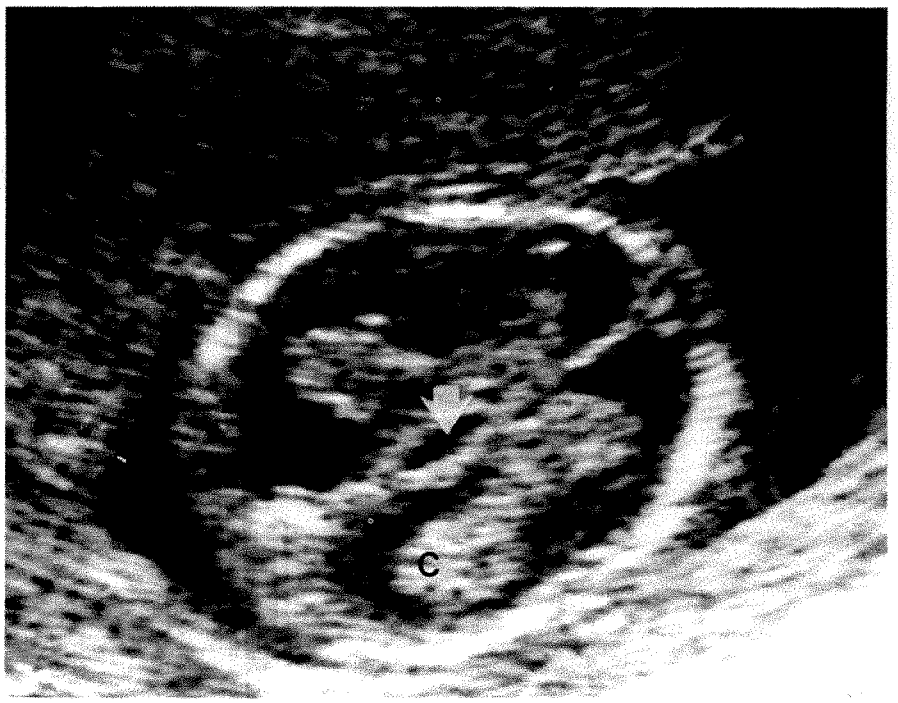


Fig. 2. Transverse scan of normal 12-week embryo head above level of thalamus. The prominent choroid plexus **(C)** is seen in the large lateral ventricular space. Third ventricle *(arrow)* is shown.



Fig. 3. Transverse scan of head at level of orbits in 12-week embryo with anencephaly.

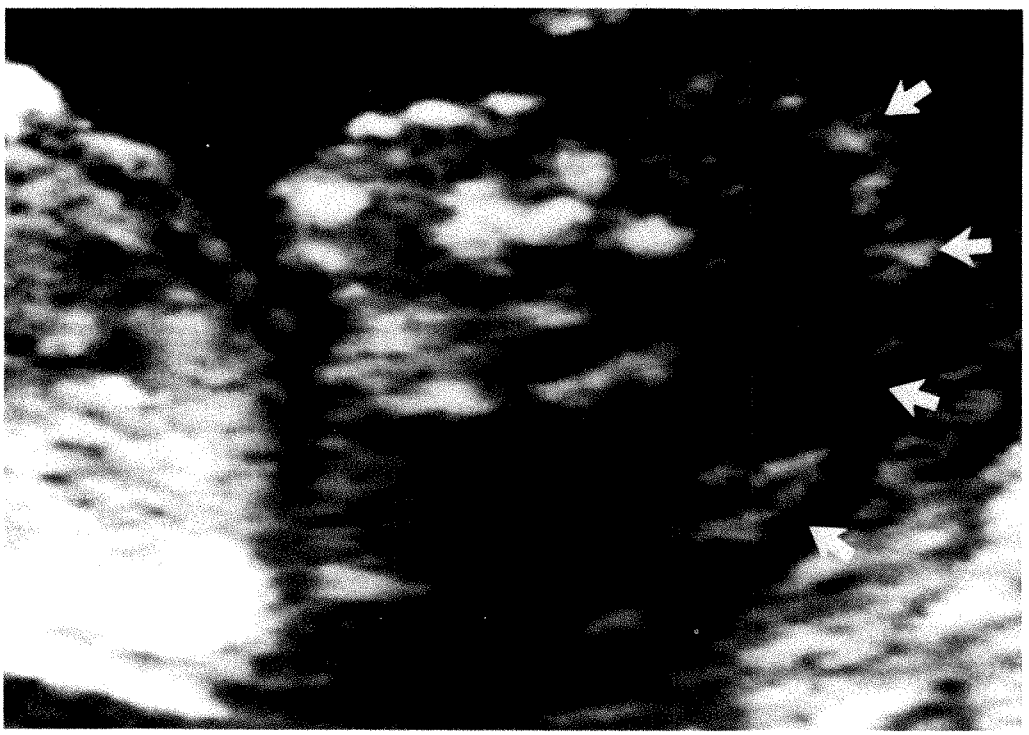


Fig. 4. Sagittal scan in 11-week pregnancy with exencephaly. Disorganized neural tissue *(arrows)* and absence of the calvarium are noted.

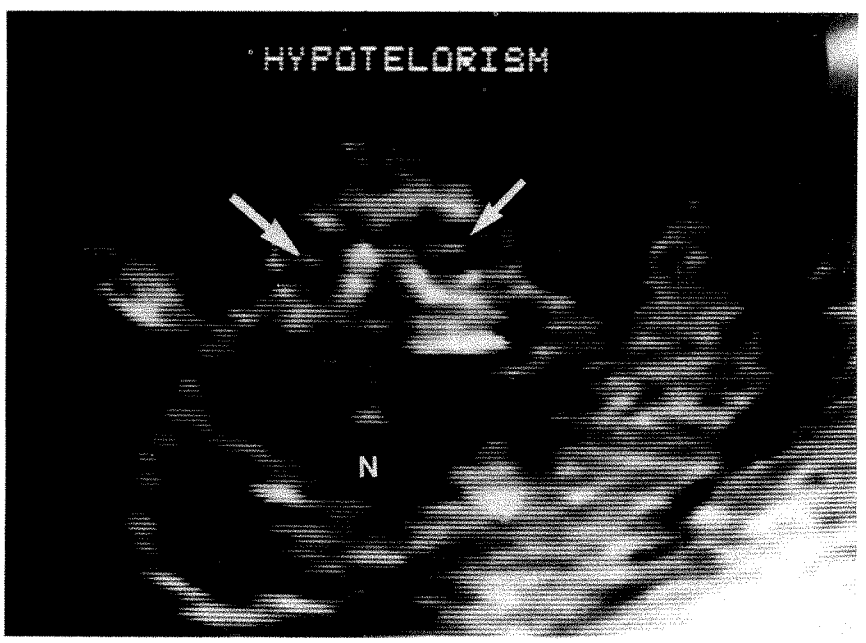


Fig. 5. Transverse scan at level of orbits showing hypotelorism *(arrows)* in a 12-week embryo with exencephaly. Disorganized neural tissue *(N)* is shown.

Ventral wall. The ventral wall of the developing embryo is apparent at 6 weeks. Physiologic herniation of the bowel into the proximal umbilical cord can be demonstrated between 8 and 11 weeks as a thickening of the cord insertion.[8-10] If the herniation is noted after 12 weeks an omphalocele should be suspected. Two omphaloceles were diagnosed in this series, both of which were associated with other anomalies. In case 3 (Fig. 7), anterior abdominal wall edema could have impeded the bowel from returning to the abdomen. In

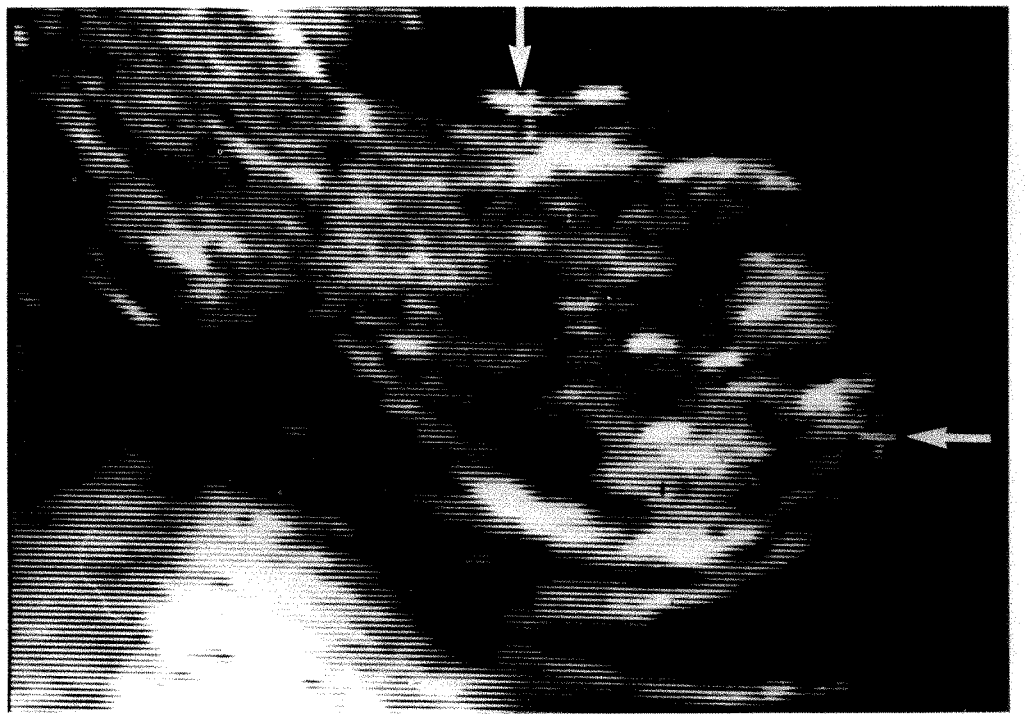


Fig. 6. Low-set ears are seen in this 12-week conceptus with nuchal cystic hygroma and trisomy 13.

case 12, hydronephrosis and an omphalocele were visualized. A large cystic dilatation in the cord represented dilated bowel. A gastroschisis (Fig. 8) was identifiable as a lateral anterior wall defect with bowel herniation remote from the cord insertion. A large ventral wall defect classified as a lateral folding defect was diagnosed in our first case based on the close proximity of the embryo to the placenta and wide short cystic cord. Since this series, we have experience with a case of gastroschisis, which was discovered at 10 weeks.

Cystic hygromas. Cystic hygromas are fluid-filled sacculations of the lateral neck and nuchal region that result from lymphatic dysplasia.[11-14] Our experience has shown that these are the most common anomaly in the first trimester. We have recently described 30 cases in a combined series,[11] grouping them by anatomic location as lateral nuchal, posterior nuchal (Fig. 9), or either location associated with hydrops (Fig. 10). The incidence of aneuploidy in this series was 53% and was not related to the anatomic location or the presence of septation. This is in contrast to reports by other authors.[14] These lesions must be differentiated from defects in the fetal spine and calvarium as well as close proximity of the embryo to the amnion and yolk sac. Since that report we have identified an embryo at 11 weeks with axillary and nuchal hygroma.

Extremities and digits. Limb paddles can be seen at 7 weeks with the long bones appearing to calcify at 10 weeks. Distinct digits are easily delineated at 11 weeks. In case 4, postaxial polydactyly was discovered retrospectively on videotape review in a fetus with cystic hygroma. The polydactyly was discovered during embryoscopic verification before termination. A case of a short limb dysplasia has been described in the first trimester.[15] In the patient with diabetes with micrognathia described in the section on facial anomalies, mesomelic dysplasia was also present and not apparent at 10.5 weeks. At that time the extremities appeared normal in size and morphologic features but were not yet mineralized. It is currently not known when specific limb dysplasias manifest.

Heart. A four-chamber view of the heart can be obtained as early as 11 weeks. Recently an atrioventricular canal defect with complete heart block was reported.[16] Despite this promising report, alterations in chamber size may not be apparent until later in pregnancy, making diagnosis of subtler defects difficult if not impossible. We are aware of two cases in which congenital heart defects were not seen in the first trimester. In one fetus at risk for Uhls syndrome, characterized by a parchmentlike right ventricle, the four-chamber view appeared normal at 13 weeks. The pregnancy was subsequently terminated for maternal reasons. Pathologic examination of the heart showed the ventricular defect was present. In a second case, transposition of the great vessels and pulmonary stenosis were not appreciated at 10 and 13 weeks but were discovered on a follow-up ultrasonographic examination at 22 weeks. Currently the sensitivity of transvaginal ultrasonography for the examination of the early heart is unclear.



Fig. 7. Transverse scan at level of abdomen shows omphalocele and hydronephrotic kidney *(arrow)*.

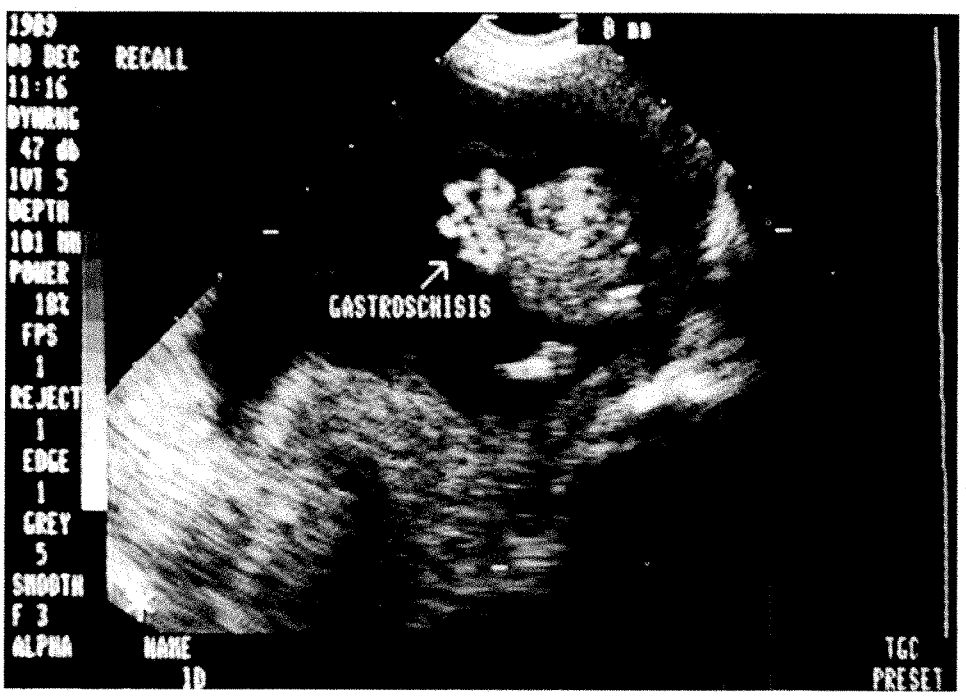


Fig. 8. Transverse scan of abdomen in 11-week embryo with gastroschisis.

Genital urinary. Kidneys and bladder may be imaged by 10 weeks. In case 13, the embryo had weekly examinations beginning at 8 weeks; at 11 weeks the renal parenchyma was noted to be hyperechoic with no obvious dilatation of the bladder. The newborn was delivered at term. A neonatal scan was performed and confirmed the suspected diagnosis of cystic dysplastic kidney disease. This series (cases 3, 5, 6, and 12) and the literature[17, 18] demonstrate the ability of ultrasonography to diagnose obstructive uropathies in the first

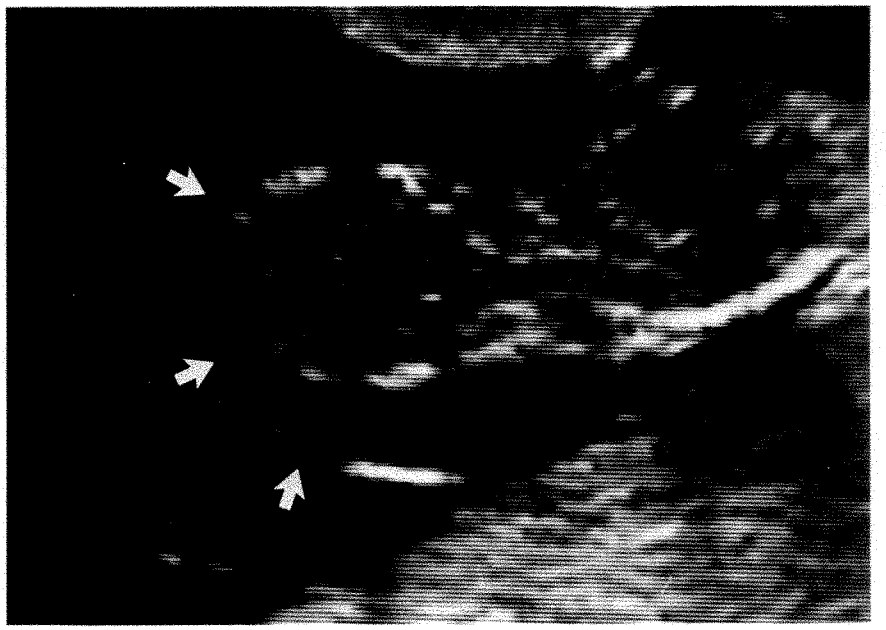


Fig. 9. Oblique scan in 11-week embryo with posterior nuchal cystic hygroma *(arrows)* in embryo with trisomy 18.

trimester. These have included megacystitis (Fig. 11) and hydronephrosis (Fig. 7). Dilatation of the bladder was diagnosed by the demonstration of a large sonolucent cystic structure in the fetal pelvis without the presence of a normal bladder. Pathologic examination was consistent with megacystitis. The early detection of renal agenesis has not been reported but might be possible by 11 weeks by nonvisualization of the kidneys and bladder. Care must be exercised not to confuse the adrenal glands with the kidneys. The adrenals are of similar size at this gestation but, unlike the kidneys, have a sonolucent cortex and dense medullary region. Anatomic differentiation of the fetal genitalia is not complete until 11 weeks, when the male phallus often can be identified. No abnormalities of this system have been recorded to date in the first trimester.

Gastrointestinal. The stomach is seen as a well-delineated hypoechoic structure inferior to the diaphragm on the left side of the abdomen at 10 to 11 weeks. Esophageal and duodenal atresia have not been reported despite the fact that many aneuploid fetuses have undergone ultrasound examinations at the time of chorionic villus sampling. We are currently following a aneuploid fetus with a classic double bubble that was detected at 13 weeks' gestation.

Placenta, umbilical cord, and yolk sac. The chorion frondosum is well demarcated at 7 weeks. A partial mole has been reported in the first trimester.[19] The placenta was noted to have multiple small sonolucent areas. Cord abnormalities in this series included a transient umbilical cord cyst that resolved without sequelae and a short cord associated with a ventral wall folding defect. In case 14, a large yolk sac measuring 2 × 2 cm (normal 0.5 × 0.5 cm) was demonstrated at 8 weeks. Fetal death was observed several days later. The embryo appeared normal by embryoscopy. Small solid yolk sacs have been observed and can be associated with impending fetal death.[1]

Twins. Identification of twins is possible as early as 5 weeks. Case 9 demonstrates the identification of monoamniotic twins, one exencephalic and the other normal. Twin reverse arterial perfusion syndrome has been reported[20] as well as conjoined twins.[21]

With the enhanced visualization afforded by transvaginal ultrasonography, care must be taken not to misinterpret normal variations in anatomy, or artifacts. Fig. 12 shows an echogenic "bowel mass" in an 11-week fetus. This echogenic structure is commonly seen and is the appearance of the normal bowel returning to the fetal abdomen from the physiologic herniation in the cord. We have also seen an echogenic area that appeared to be in the frontal lobe in the calvarium in an 11-week euploid embryo with cystic hygromas. Both the hygroma and "lesion" subsequently resolved. The newborn was normal.

This study demonstrates the applicability of ultrasonography for the antenatal diagnosis of structural anomalies in the first trimester of pregnancy and illus-

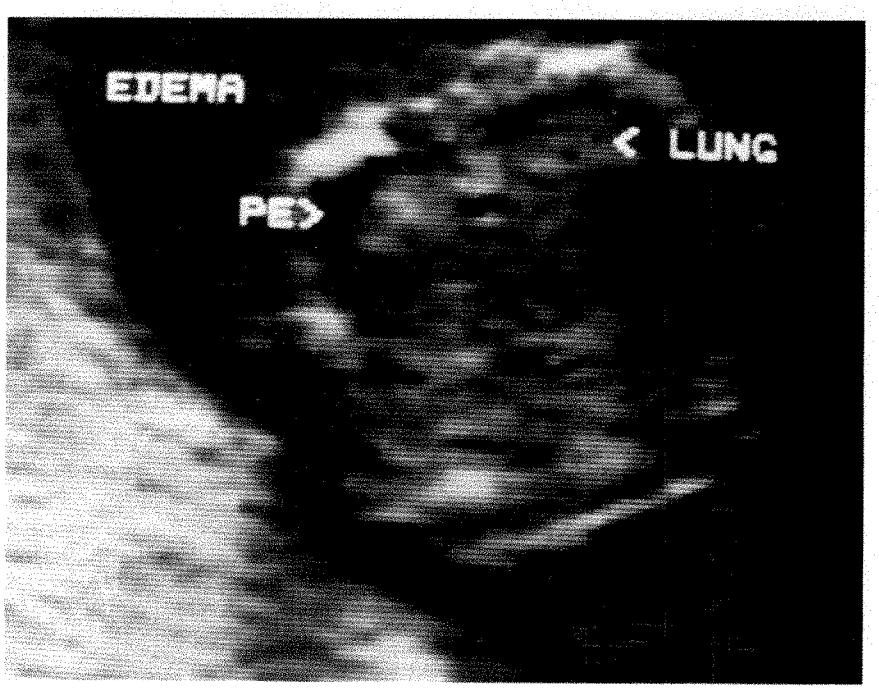


Fig. 10. Transverse ultrasonographic scan through 13-week embryo with posterior cystic hygromas and hydrops. Pleural effusions *(PE)* are shown.

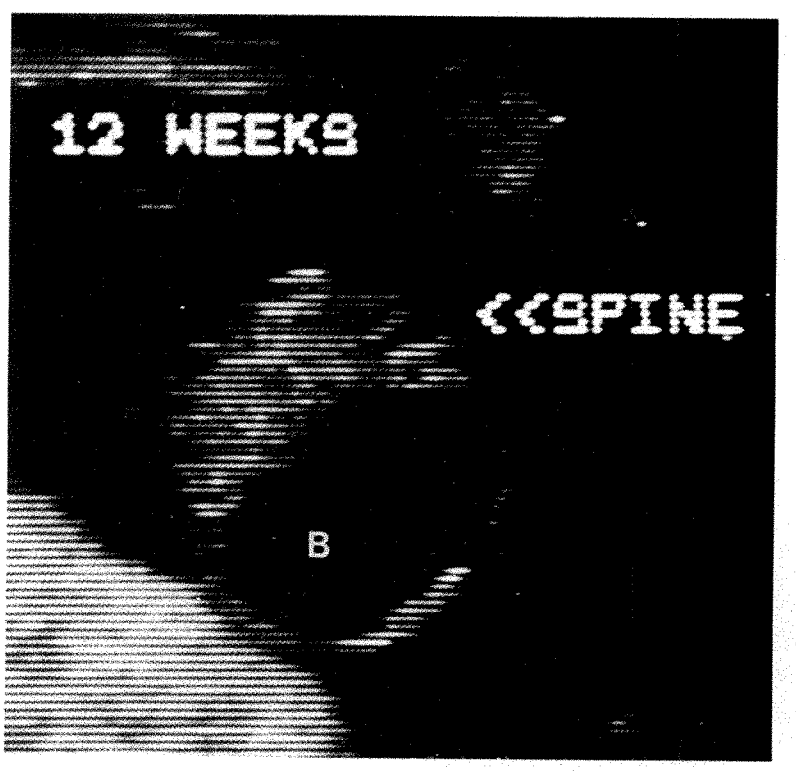


Fig. 11. Transverse scan in 12-week embryo with bladder outlet obstruction. Bladder *(B)* is visualized.

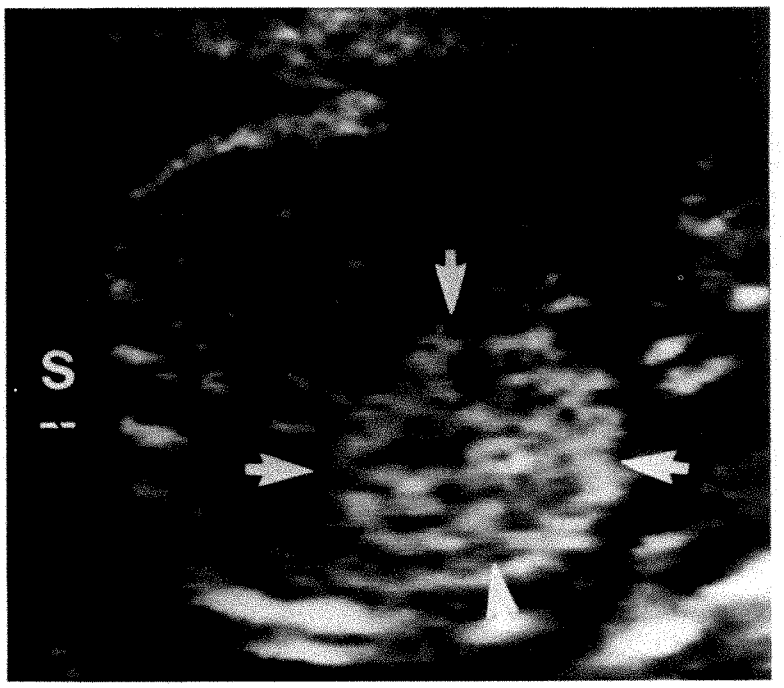


Fig. 12. Transverse scan in normal 12-week embryo with prominent bowel *(arrows)*. Spine *(S)* is shown.

trates some limitations. The incidence of a structural anomaly was surprisingly low. This could reflect a high number of low-risk patients that were examined. It is noteworthy that 22 of the 33 patients with an anomaly (66%) were at "high risk."

The mean gestational age at the time of diagnosis of the anomaly in this study was 11 weeks. This reflects limitations in the normal developmental sequence, delayed manifestation of disease (as in chamber dilatation in congenital heart disease), or late referrals.

We believe it is imperative to correlate pathologic and ultrasonographic findings especially during the early investigating period of first-trimester detection while establishing diagnostic criteria. Currently, few reports in the literature have such data available. Because routine suction curettage often makes pathologic confirmation difficult, prostaglandin abortion[16] or embryoscopy[4] can be used as an alternative.

Because of the limited experience with early antenatal screening of structural defects, serial scans should be performed before excluding an anomaly in a pregnancy at risk. We agree that experience with early ultrasonography and a thorough understanding of embryology must be gained before its application in first-trimester diagnosis.[22] The study design and the number of patients in the study do not allow a statement to be made about the sensitivity of the technique for the diagnosis of specific anomalies, but this and other preliminary data[7] suggest a future role for fetuses at risk. Prenatal diagnosis of structural anomalies will move into the first trimester.

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Acromegaly first diagnosed in pregnancy: The role of bromocriptine therapy

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We report a case of acromegaly diagnosed in the second trimester of pregnancy. Bromocriptine (7.5 mg per day) corrected visual field defects and suppressed prolactin secretion but did not reduce fasting growth hormone levels. We propose that suppression of physiologic lactotroph hyperplasia by bromocriptine may permit noninvasive management of pituitary adenomas during pregnancy. (Am J Obstet Gynecol 1990;163:477-8.)

Key words: Acromegaly, pregnancy, bromocriptine

Pregnancy in a woman with untreated acromegaly is very rare and to our knowledge has been adequately documented only once previously.[1] We report a woman whose acromegaly, complicated by optic chiasmal compression, was first recognized in pregnancy.

Case report

A gravida 2, para 1 woman aged 32 years was first seen at 18 weeks' gestation. Her first pregnancy 7 years previously was uneventful. Subsequently she had become hypertensive, had noticed increasing shoe size and abnormal sweating, and carpal tunnel compression developed that required surgery. Menses were irregular for 3 years before conception. From 16 weeks' gestation she experienced intermittent episodes of blurred vision. She had a coarse face, prognathism, and sausage fingers. Visual fields were normal by perimetry.

The pituitary fossa was not enlarged but the floor and posterior clinoids were eroded. Fasting growth hormone (GH) levels were high (37 mU/L; normal range, <10 mU/L) and failed to suppress with administration of glucose (peak GH was 44 mU/L), consistent with a diagnosis of acromegaly. The glucose tolerance test results showed diabetes. Prolactin levels were appropriate for her stage of pregnancy, and thyroid and adrenal function were normal.

Visual symptoms continued and minor abnormalities of red fields appeared on perimetry. Examination of visual-evoked responses showed prolonged central field latencies. An intrasellar tumor was shown by computerized tomography. Although no suprasellar extension was seen, concern about optic nerve compression prompted administration of bromocriptine in doses that were increased to 7.5 mg/day. Visual symptoms and field abnormalities resolved within 2 weeks. Prolactin levels were suppressed by bromocriptine without significant changes in GH levels (Fig. 1). A normal infant was delivered by cesarean section at 39 weeks' gestation. Bromocriptine was continued for 2 weeks postpartum to suppress lactation. Despite this there was an immediate postpartum increase in fasting GH levels and a significant reduction in prolactin levels.

Results of a repeat glucose tolerance test at 7 weeks postpartum were nondiabetic. Basal GH (108 mU/L) and peak GH (186 mU/L) levels were higher than those in pregnancy and basal prolactin levels (11 pmol/L) were normal. An intrasellar maroadenoma was confirmed by a second computerized tomography scan and an acidophil tumor resected transsphenoidally. The pituitary fossa was subsequently irradiated.

On follow-up, clinical signs of acromegaly and menstrual irregularity persisted but excessive sweating resolved. Serial glucose tolerance tests showed progressive decreases in GH levels.

Comment

Diagnosis of acromegaly requires demonstration of abnormal GH secretion, usually by elevated fasting levels and failure to suppress (or a paradoxical rise) with glucose administration. Earlier reports of acromegaly occurring in pregnancy have usually failed to provide such documentation or have been confounded by prior treatment. GH is less responsive to stimulation in normal pregnancy[2] and this dampened response, which was apparent in our patient but not in that previously reported,[1] may complicate the diagnosis of acromegaly. Although insulin-like growth factor 1 levels are raised in acromegaly and correlate better with disease activity than do GH measurements, the normal rise in insulin-like growth factor 1 levels

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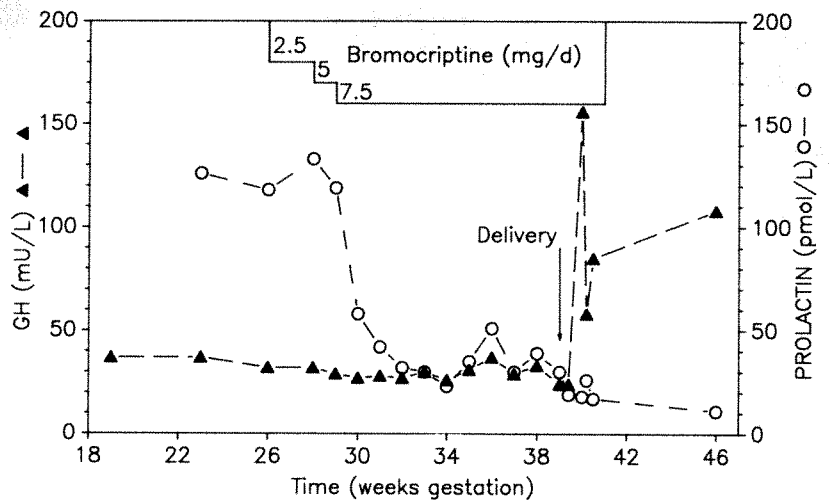


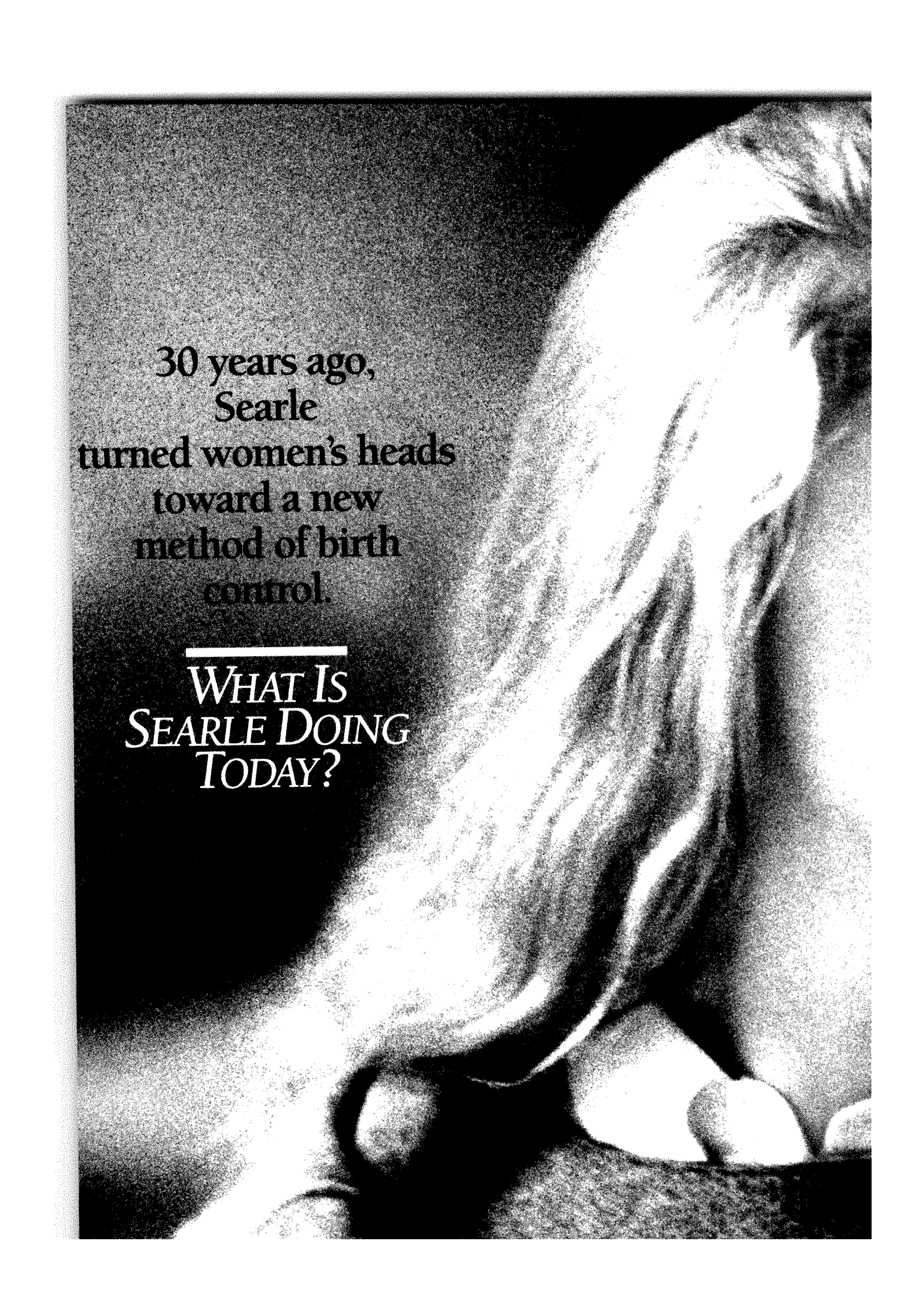
Fig. 1. Effect of bromocriptine on serial fasting growth hormone and prolactin levels during pregnancy and in early postpartum period. Fasting growth hormone normal range is <10 mU/L.

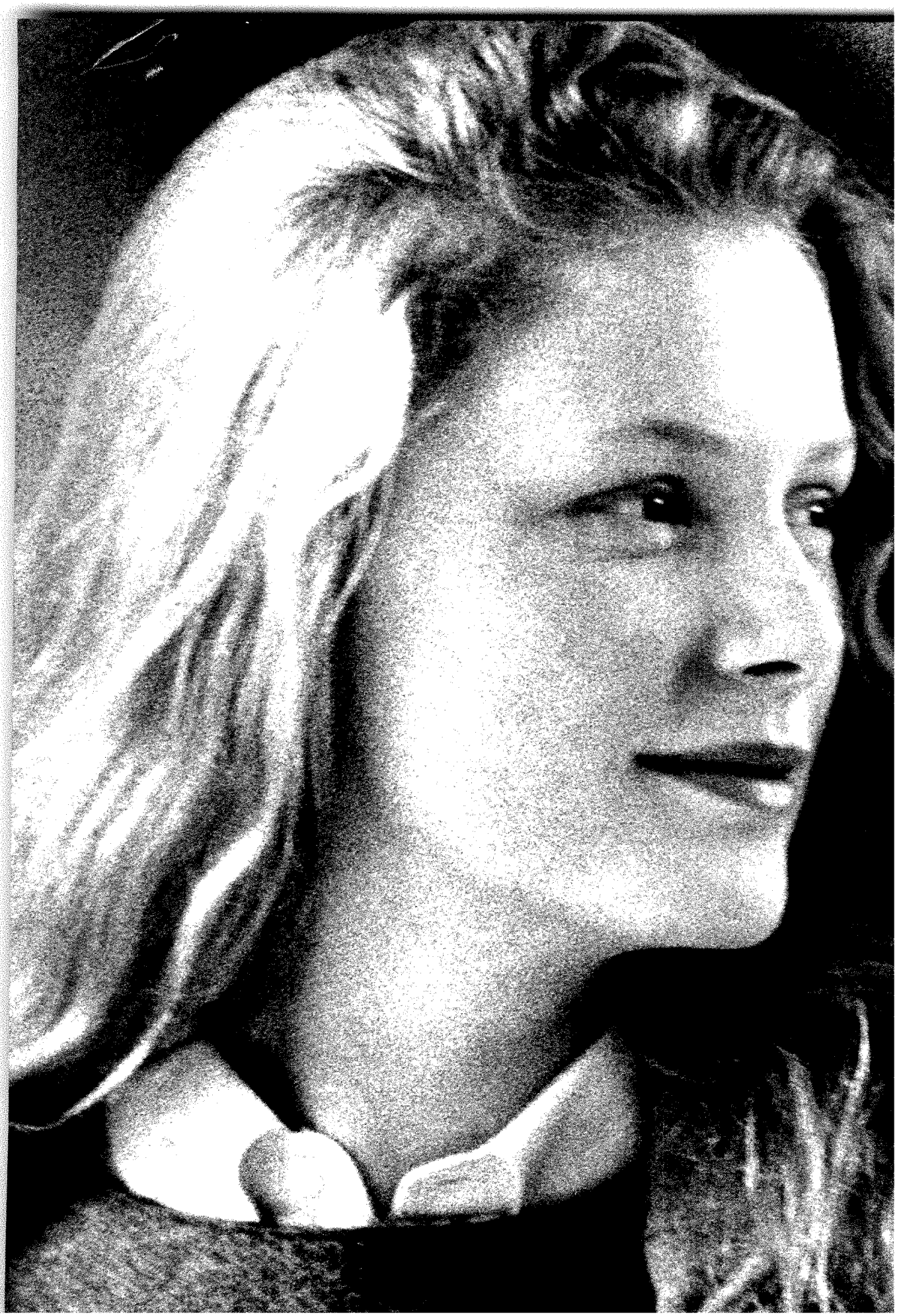
seen in pregnancy reduces the diagnostic utility of this test.

Tumor growth and compression of adjacent structures is a major potential complication of a pituitary macroadenoma in pregnancy. Our patient had evidence of optic nerve compromise but the suppression of normal pregnancy levels of prolactin by bromocriptine without associated changes in GH level suggests that resolution of visual field abnormalities resulted from suppression of physiologic hypertrophy of normal pituitary tissue rather than by tumor shrinkage per se.

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1. *Thromboembolic disorders and other vascular problems:* Increased risk of thromboembolic and thrombotic disease associated with OCs is well established. A British study showed increased risk for fatal venous thromboembolism (TE). British and U.S. studies showed increased risk for nonfatal disease. U.S. studies showed increased risk for stroke. OC users were 2-11 times more likely to manifest these diseases without evident cause. In a study of idiopathic deep vein thrombosis and pulmonary embolism (PE), projected hospitalization rates for ages 16-40 were 47/year/100,000 users and 5 for nonusers. Overall excess mortality from PE or stroke was 1.3-3.4 deaths/year/100,000 users and increased with age. *Cerebrovascular Disorders:* In a study of stroke with and without predispositions, risk of hemorrhagic stroke was 2 times greater and thrombotic stroke 4.0-9.5 times greater in users. Mortality trends in 21 countries indicate that changes in cardiovascular mortality were associated with changes in OC prevalence. The Royal College of GPs (RCGP) reported on its prospective study: "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." A 1981 analysis showed a 4-fold increased mortality in users from circulatory diseases, mainly myocardial infarction (MI) and hemorrhagic stroke. Excess mortality was associated with age and smoking. A 1983 analysis showed elevated cerebrovascular disease, increasing with use to 8 yrs, including cerebral thrombosis or embolism and TIA. Peripheral arterial disease and MI were increased. Women over 30 had more arterial disease, being greatest in smokers. Arterial case-fatality was 2-3 times greater for users who smoked. Family Planning Assoc. (FPA) found significant association between OC use and stroke; increased risk for venous thrombosis and PE was 4-fold and statistically significant. Mortality from nonrheumatic heart disease was greater in ever-users. In the Walnut Creek Study, subarachnoid hemorrhage risk was associated with smoking, age, and OC use. *Myocardial Infarction:* Increased risk of MI associated with OCs was reported in Britain, as previously suspected. The morbidity study found the greater the number of risk factors for coronary artery disease (smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk, regardless of OC use. OCs were an additional risk factor. Excess rate of fatal MI was 3.5/year/100,000 users aged 30-39 and 20 for ages 40-44. (These are based on British statistics with acute MI death rates 2-3 times less than the U.S. Similar estimates for the U.S. are 25.7 for users aged 30-39 with predispositions vs 1.5 without; for ages 40-44, 86.2 vs 5.1.) Excess hospitalization rate for nonfatal MI in Britain was 3.5/year/100,000 users aged 30-39 and 47 for ages 40-44. Smoking is a major predisposing condition to MI. In terms of relative risk, nonsmoking OC users are twice as likely to have fatal MI as nonsmoking nonusers. Smoking users have a 5-fold greater risk than nonsmoking users, but a 10-12-fold greater risk than nonsmoking nonusers. Amount of smoking is an important factor. In determining importance of these risks, give serious consideration to rates in table below. Importance of other predispositions cited above in determining relative and absolute risks has not been quantified; it is likely the same synergism exists, but perhaps to a lesser extent. U.S. studies similarly relate MI, OCs, smoking, and age.

Estimated Mortality Rate from Myocardial Infarction per 100,000 Women/Year

	Aged 30-39:	*Users*	*Nonusers*	*Aged 40-44:*	*Users*	*Nonusers*
All smokers		10.2	2.6		62.0	15.9
	≥15 cigarettes daily	13.0	5.1		78.7	31.3
	<15 cigarettes daily	4.7	0.9		28.6	5.7
Nonsmokers		1.8	1.2		10.7	7.4
Smokers and nonsmokers		5.4	1.9		32.8	11.7

Risk of Dose: Reports of TE after use of OCs with ≥50 mcg estrogen received by drug safety committees in Britain, Sweden, and Denmark were compared with distribution expected from market research sales estimates. A positive correlation was found between estrogen dose and reporting of TE, including coronary thrombosis, in excess of that predicted by sales. OCs with ≥100 mcg estrogen were associated with higher TE risk than those with 50-80 mcg. Estrogen quantity may not be the sole factor; influence of progestogens was not considered, which may be responsible for certain discrepancies in the data. No significant differences were noted between OCs containing same estrogen dose nor between ethinyl estradiol and mestranol. In Britain certain TE conditions were associated with progestogen or estrogen dose. In Sweden reports of TE decreased when higher estrogen doses were no longer prescribed. Studies on TE risk with progestogen-only OCs have not been done. Cases have been reported for these; they are not presumed free of risk. In a U.S. case-controlled study, relative risk of OC use 1 month before hospitalization for various types of TE was calculated. If relative estrogenic potency and possible influence of different progestogens are ignored, OCs may be divided into those with <100 mcg and those with ≥100 mcg estrogen. For all cases combined, larger doses were associated with only slightly higher risk; for idiopathic cases risk was doubled with larger doses, but confidence limits overlapped and differences were not significant. Apparently there was less increased risk for cases with predispositions. In FPA study no nonhemorrhagic strokes occurred with <50 mcg estrogen, vs 13 with higher doses. Latter group also had more venous TE. TE risk in users and nonusers increases with age. OCs have been considered an independent risk factor. Decreased HDL, which relates to increased myocardial ischemia, occurs with high progestational activity. Consider amount of both steroids in choosing OC. *Persistence of Risk* after OC discontinuation was reported for circulatory disease, nonrheumatic heart disease, and cerebrovascular disease, including subarachnoid hemorrhage, cerebral thrombosis, and TIA. *Excess Mortality from Circulatory Diseases:* A U.K. prospective study estimated annual mortality from circulatory diseases for OC users and nonusers by age, smoking, and duration of use. Excess mortality was 23/100,000 users (2 and 10 for ages 25-34, 15 and 48 for ages 35-44, 41 and 179 for ages >44, for nonsmokers and smokers, respectively). Risk was significant only for smokers over 34. Most deaths were due to subarachnoid hemorrhage or ischemic heart disease. Risk for ever-users rose with parity. One study estimated risk of death with various contraceptive methods, each estimate including risk of method (eg, TE for OCs) plus risk due to pregnancy or abortion in cases of method failure. This latter risk varies with effectiveness. It concluded mortality with all methods is low and below that of childbirth, except for OC users over 40 who smoke. Heavy smokers have double the risk of smokers, light smokers about half. Mortality with OC use in nonsmokers over 40 is higher than with any other method in that age group. Lowest mortality is with condom or diaphragm backed up by early abortion. Risk of TE and thrombotic disease with OCs increases with age after 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia, and especially cigarette smoking. Based on current data, the chart gives gross estimates of risk of death from circulatory disorders associated with OCs:

Risk is: A—very high; B—high; C—moderate; D—low.	Age:	<30	30-39	≥40
Heavy smokers (≥15/day)		C	B	A
Light smokers (<15/day)		D	C	B
Nonsmokers, no predispositions		D	C,D	C
Nonsmokers, with predispositions		C	C,B	B,A

Be alert to earliest manifestations of TE disorders (eg, thrombophlebitis, PE, cerebrovascular insufficiency, coronary artery disease, MI, retinal thrombosis, mesenteric thrombosis). Should any be suspected, discontinue OCs immediately. A 4-7-fold increased risk of postsurgery TE was reported in users; if feasible discontinue OCs at least 4 weeks before surgery or in prolonged immobilization. Before resuming OCs, weigh risks of postsurgery TE complications against contraceptive needs. RCGP reported higher incidence of superficial and deep vein thrombosis in users, the former correlated with progestogen dose. Varicose veins have little effect on development of deep vein thrombosis. **2.** *Ocular lesions:* Neuro-ocular lesions such as optic neuritis or retinal thrombosis have been associated with OCs. Discontinue if there is unexplained, gradual or sudden, partial or complete loss of vision; proptosis or diplopia; papilledema; or evidence of retinal vascular lesions. Institute diagnostic and therapeutic measures. **3.** *Carcinoma:* Long-term estrogen in certain animals increases carcinomas and/or nonmalignant neoplasms, such as those of breast, uterus, cervix, vagina, ovary, liver, pituitary. Some synthetic progestogens, none currently in OCs, increase incidence of benign and malignant mammary nodules in dogs. Estrogens increase risk of human endometrial carcinoma. In case-controlled studies, increased risk (2.2-13.9 times) associated endometrial carcinoma with prolonged estrogen for menopausal symptoms. Risk was independent of other known risk factors and depended on duration of use and dose. This is supported by increased endometrial cancer incidence since 1969 in areas with cancer-reporting systems, which may be related to expanding estrogen use. There is no evidence that natural estrogens are more or less hazardous than synthetics. Of the first 30 cases of endometrial carcinoma in OC users under 40, those without predispositions occurred nearly always with no-longer-marketed sequential OCs. No statistical association is reported suggesting increased end cancer with combination or progestogen-only OCs. Studies show no increased breast cancer with OCs or estrogens. H greater risk was noted in OC users with benign breast disease or long-term (2-4 years) use. One study found greate breast cancer with >4 years OC use prior to first full-term pregnancy. Risk of breast cancer with menopausal estrog and further increased with duration of follow-up. OCs or estrogen were related to breast cancer in connection with o factors and in various subgroups. Decrease in benign breast tumors in OC users is well known. Some studies su increased risk of cervical dysplasia, CIN, erosion, and carcinoma in long-term users. Cervical microglandular hyperpl been reported. In summary, there is no consistent evidence from human studies of increased cancer risk with OC surveillance is, however, essential. In undiagnosed persistent or recurrent abnormal vaginal bleeding, consider nonfu causes and take diagnostic measures to rule out malignancy. Carefully monitor users with strong family history c cancer or with breast nodules, fibrocystic disease, recurrent cystic mastitis, abnormal mammograms, or cervical d **4.** *Hepatic adenomas, etc,* have been associated with OCs. In 1 study OC formulations with high "hormonal potenc associated with higher risk, as was age over 30. Though benign, these lesions may rupture and cause fatal hemope in short- or long-term users. Two studies related risk to duration of use, being much greater after ≥4 years. Long- users have an estimated adenoma incidence of 3-4/year/100,000. Consider such lesions in users with abdomi tenderness, mass, or shock. About 25% present with abdominal masses, up to half with acute hemoperitoneum. R and lab studies may not be helpful; liver scans may show local defect. Hepatic arteriography or CAT may b Hepatocellular carcinoma risk is increased 7-20 times in users for 8 or more years. Bile duct cancer may occur with **5.** *Use in or immediately preceding pregnancy, birth defects, malignancy in offspring:* Estrogens or progestogens dur pregnancy may seriously damage offspring. Females exposed in utero to DES and other nonsteroidal estrogens m increased risk of vaginal or cervical cancer. Though OCs may not enhance this risk, monitor such patients carefully. F 90% of DES-exposed women develop benign vaginal or cervical adenosis, which could be premalignant. DES- daughters have more unfavorable pregnancy outcomes. Males so exposed may develop urogenital and sperm defect estrogens may mimic DES. Reports relate fetal exposure to female sex hormones and congenital anomalies, eg, VAC vertebral, anal, cardiac, tracheoesophageal, renal, and limb defects. There appears preferential expression by male was a 4.7-fold increased risk of limb-reduction defects in infants exposed in utero to sex hormones (OCs, hormonal wi pregnancy tests, or treatment for threatened abortion). Some exposures were very short; being only a few days. Cardio defects in children exposed to female hormones, including OCs, during early pregnancy occurred in 18.2/1,000 compared to 7.8 for those unexposed (P<.05). Female hormone exposure in utero was associated with testicular anc cancer. More twinning was reported in conceptions shortly after OC discontinuance. Female sex hormones were threatened or habitual abortion, but there is considerable evidence estrogens are ineffective and no evidence progr are effective. Triploidy and possibly other polyploidy may be increased in abortuses from women becoming pregna post-OC. These almost always abort spontaneously. It is unknown if spontaneous abortion is increased soon after OCs. Increased chromosome aberrations have been reported. Safety of OCs in pregnancy has not been demonstrat out pregnancy in using OCs and always consider it if withdrawal bleeding does not occur. If 2 consecutive periods are rule out pregnancy before continuing. If user deviates from regimen, consider pregnancy at first missed period and OCs. If pregnancy is confirmed, stop OC and apprise patient of potential fetal risks and discuss continuation of pre Users discontinuing for pregnancy should use alternative contraception for 3 months before attempting to conceive this is not based on precise information. Do not use progestogen-only or progestogen-estrogen drugs as pregnanc **6.** *Gallbladder disease* risk, surgically confirmed, appeared after 2 years' use and doubled after 4-5 years in 1 appeared in 6-12 months' use in another. Bile duct cancer has been reported. **7.** *Carbohydrate and lipid metabolism:* De glucose tolerance occurs in a significant number of users; carefully observe diabetic and prediabetic patients. Triglyc total phospholipids, and lipoproteins may increase. **8.** *Elevated blood pressure* (BP) occurs in some users in a few and degree may relate to progestogen dose. Hypertension prevalence in users is not higher in the first year, but ri with longer exposure; in the 5th year it is 2½–3 times the first year. Age is strongly correlated with hypertension i Those with history of elevated BP (hypertension), preexisting renal disease, history of toxemia or elevated BP in pre familial tendency to hypertension or its consequences, or history of excessive weight gain or fluid retention during m cycles may be more likely to develop elevated BP on OCs and should be monitored closely. Even though elevated BP in "normal" range, do not ignore implications. Follow closely, particularly those with other risk factors for cardio disease or stroke. High BP may or may not persist after stopping OCs. **9.** *Headache:* Onset or exacerbation of mig development of headache of a new pattern that is recurrent, persistent, or severe requires stopping OCs and evaluatin **10.** *Bleeding irregularities:* Breakthrough bleeding (BTB), spotting, and amenorrhea are frequent reasons for discontir BTB, as in all cases of irregular bleeding, consider nonfunctional causes. In undiagnosed persistent or recurrent bleed out pregnancy or malignancy. If pathology is excluded, time or change to another product may suffice. Change to a estrogen OC only when necessary as this may increase thromboembolic risk. Those with history of oligomeno secondary amenorrhea or without established regular cycles may be anovulatory or amenorrheic after discontinuing with such problems should be so informed and other methods encouraged. Post-use anovulation, possibly prolong occur in women without previous irregularities. Higher incidence of galactorrhea and of pituitary tumors has been as with postpill amenorrhea. One study reported 16-fold increased prevalence of pituitary prolactin-secreting tumors in with postpill amenorrhea when galactorrhea was present. **11.** *Ectopics:* In failures with combination OCs, the ratio of to intrauterine pregnancies is no higher than in nonusers. **12.** *Breast feeding:* OCs may decrease quantity and quality A small fraction of OC steroids appears in milk. Effects if any on child are unknown. If feasible defer OCs until after **13.** *Infertility* may occur after discontinuing OCs. While impairment diminishes with time, there is still an appreciable di in nulliparas aged 25-29 after 30 months; difference is negligible after 48 months. In nullips aged 30-34 impairment to 72 months and is more severe for 2-year users. In paras aged 25-34, difference is negligible after 30 months. **Pre** Conduct complete history and physical prior to OC use and annually thereafter. Include breasts, abdomen, and pel BP, Pap, and lab tests. Preexisting uterine leiomyomata may enlarge. Mental depression may occur; with positive observe carefully and discontinue if serious recurrence. Fluid retention may occur; prescribe cautiously and monitor in convulsive disorders, migraine, asthma, or cardiac, hepatic, or renal dysfunction. History of jaundice in pregnancy ir risk of recurrence on OCs; observe carefully and discontinue if it occurs. Cholestatic jaundice occurred after troleandomycin use. OC/cyclosporine combination may be hepatotoxic. Steroids may be poorly metabolized in liver dys and should be given cautiously. Tryptophan metabolism may be disturbed and result in pyridoxine deficiency; megal anemia has been reported. Serum folate may be depressed and may be exacerbated in post-OC pregnancy. Advise pat of OC use when submitting specimens. Endocrine and liver function tests may be altered; repeat abnormal tests after s for 2 months. These have been observed: increased BSP retention and other abnormalities in liver function tests; in prothrombin and coagulation factors VII, VIII, IX, X; decreased antithrombin III, increased platelet aggregability; in thyroid-binding globulin leading to increased circulating total thyroid hormone (PBI, T_4); decreased T_3 uptake, unalte T_4, decreased pregnanediol excretion; reduced metyrapone response; increased blood transcortin, corticosteroid, trigl phospholipid, reduced serum folate; impaired glucose tolerance; altered plasma trace minerals. Influence of prolonged on pituitary, ovarian, adrenal, hepatic, or uterine function, or on immune response not established. OCs may mask climacteric. Cervical chlamydial and gonorrheal prevalence is increased; do not assume OC protects against chlamyc HIV seropositivity was associated with OC use. *Information for patients.* See patient labeling. *Drug interactions.* OC effect may be decreased and more BTB occur with rifampin, isoniazid, ampicillin, neomycin, penicillin V, tetracycline, chloramp sulfonamides, nitrofurantoin, griseofulvin, barbiturates, phenytoin, carbamazepine, primidone, phenylbutazone, ana tranquilizers, antimigraines. OCs may alter effectiveness of oral anticoagulants, anticonvulsants, tranquilizers, antidepressants, antihypertensives, theophylline, caffeine, vitamins, hypoglycemics, clofibrate, glucocorticoids, acetami **Adverse reactions:** Increased risk of the following serious adverse reactions has been associated with OCs: thrombo and thrombosis; pulmonary embolism; arterial thromboembolism; Raynaud's disease, myocardial infarction; c thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; Budd-Chiari syndrome; adenomas and other hepatic lesions, with or without intra-abdominal bleeding; liver cancer, congenital abnormalities evidence of association between the following and OCs, though confirmatory studies have not been done: me thrombosis; neuro-ocular lesions, eg, retinal thrombosis and optic neuritis. The following are believed drug related: vomiting, gastrointestinal symptoms, BTB, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during a use, infertility post-OC, edema, chloasma or melasma, which may persist post-OC, breast changes (tenderness, enlar secretion), weight changes, change in cervical erosion and secretion, endocervical hyperplasia, lactation decrease, ch jaundice, migraine, enlarged uterine leiomyomata, allergic rash, mental depression, reduced carbohydrate tolerance, candidiasis, change in corneal curvature (steepening), intolerance to contact lenses. Association not confirmed or refu premenstrual-like syndrome, cataracts, libido changes, chorea, appetite changes, cystitis-like syndrome, headache, pare nervousness, dizziness, auditory disturbances, rhinitis, fatigue, backache, hirsutism, scalp hair loss, erythema multi nodosum, hemorrhagic eruption, herpes gestationis, hidradenitis suppurativa, hemolytic uremia, malignant hyper impaired renal function, acute renal failure, sometimes irreversible, itching, vaginitis, porphyria, PVCs, abnorm pulmonary hypertension, TTP, anemia, pancreatitis, hepatitis, colitis, Crohn's disease, gingivitis, dry socket, lupus erythem rheumatoid arthritis, pituitary tumors (eg, adenoma) with amenorrhea and/or galactorrhea after use, malignant me endometrial, cervical, breast, and bile duct carcinoma. **Acute overdosage:** Serious ill effects have not been report large acute doses of OCs in young children. Nausea and withdrawal bleeding might occur. **Important note: Co prescribing information should be consulted prior to use and is available on request.**

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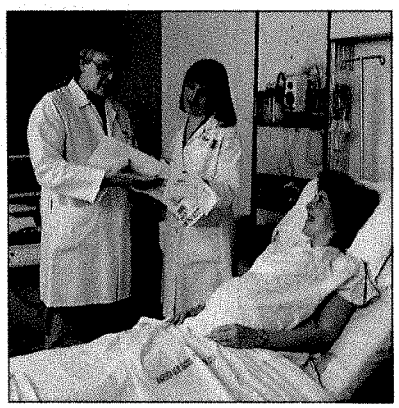
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Epithelial cells from normal human endometrium express a tumor-associated glycoprotein (TAG-72) epitope in vitro

Kevin G. Osteen, PhD,[a, b] Ted L. Anderson, PhD,[a, b] Joel T. Hargrove, MD,[a] George A. Hill, MD,[a] and Fred Gorstein, MD[b]

Nashville, Tennessee

Monoclonal antibody B72.3 identifies a tumor-associated glycoprotein (TAG-72) epitope derived from a human breast carcinoma metastasis. Recently, expression of this epitope was noted in normal endometrium during the secretory, but not proliferative, menstrual interval. In light of known hormonal control of normal endometrial growth and differentiation, we investigated in vitro expression of TAG-72 epitope in purified endometrial epithelium cultured under serum-free conditions on Matrigel biomatrix. Cells from secretory endometrium exhibited homogeneous tumor-associated glycoprotein 72 epitope expression. Unexpectedly, epithelium from the proliferative interval developed expression after 5 to 6 days of culture. Epithelial cells from both intervals maintained expression over 12 days of culture without exogenous estradiol and progesterone. Spontaneous, uniform expression of tumor-associated glycoprotein 72 epitope by normal endometrial epithelial cells in vitro is in marked contrast to the cyclic, heterogeneous expression observed in vivo. Such expression also differs from published in vitro observations of cancer cell lines that express this epitope. (Am J Obstet Gynecol 1990;163:479-84.)

Key words: Endometrium, epithelium, matrix, tissue culture, differentiation, tumor epitope

Monoclonal antibody B72.3 is directed against a high molecular weight membrane-associated determinant extracted from a breast tumor metastasis.[1] Shown to be immunoreactive with carcinomas of the breast, ovary, colon, and uterus,[2-5] this antibody was originally reported to be nonreactive with normal adult epithelium from a variety of tissues.[3, 4] Subsequently, however, monoclonal antibody B72.3 was reported to recognize normal human endometrial epithelium, but only during the secretory menstrual interval.[5]

The antigen recognized by monoclonal antibody B72.3 has been designated tumor-associated glycoprotein 72 (TAG-72), which has not been well characterized. A partial purification of TAG-72 from a xenograph of a colon cancer cell line (LS-174T) in athymic mice found the epitope to be a neuraminidase-sensitive mucin-like molecule.[6] Recent studies indicate that monoclonal antibody B72.3 reacts with the core region of O-linked sialosyl-2→6α-N-acetylgalactosaminyl (sialosyl-Tn) epitope.[7]

Although the degree of TAG-72 expression in tumor cell xenografts approximates that observed in tumor masses in situ, this level of expression is not exhibited by tissue cultures of similar tumors.[8] Maintenance of TAG-72 expression by LS-174T cells in vitro is poor, and appears to depend on the three-dimensional architecture of cells in the culture system; LS-174T cells grown in agar gels expressed a 10-fold higher level of TAG-72 compared with cells grown on plastic.[8]

Our attention has focused on the stage-specific recognition of normal human endometrium by monoclonal antibody B72.3, which promises to be a useful differentiation marker in this tissue and may provide unique opportunities to examine the regulation of TAG-72 epitope expression. To this end, methods have been developed to isolate, with high purity and viability, glandular epithelium from normal human endometrium.[9] When cultured appropriately on biomatrix, these cells were found to establish and maintain an in vivo—like architecture and polarity.[10] In the present study we examined the pattern of B72.3-reactive epitope expression in vitro by normal human endometrial epithelium obtained during proliferative versus secretory intervals of the menstrual cycle, and we compared such expression with that observed in vivo.

Material and methods

Sources of tissue. Endometrial biopsy samples were obtained from normally cycling women for indications

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6/1/21798

not associated with uterine dysfunction during the mid-proliferative (cycle days 5 to 10; $n = 7$) and mid-to-late secretory (cycle days 21 to 26; $n = 9$) intervals. All samples were obtained and used with prior approval of the Vanderbilt University Committee for the Protection of Human Subjects. Specimens were collected in a 1:1 mixture of phenol red-free Dulbecco's modified Eagle's medium and Ham's nutrient mixture F-12 with 15 mol/L hepes, antibiotics, and 10% charcoal-stripped fetal bovine serum (DME/F-12/FBS) for transport to the laboratory. A portion of each sample was placed in 4% buffered formalin for routine histologic evaluation and for immunohistochemical studies as described later.

Purification of epithelial cells. Endometrial biopsy tissue was dissected into small pieces (1 to 2 mm^3) and washed by centrifugation (400 *g*) in fresh medium to remove debris and most blood cells. Epithelial cell isolation was accomplished by a procedure involving selective enzymatic digestion, filtration, unit gravity sedimentation, and selective plating, as previously described.[9] Briefly, tissues were incubated with DME/F-12 containing 0.5% collagenase, 0.02% deoxyribonuclease, and 2% chicken serum for 1 hour at 37° C in a shaking water bath. Cell clumps were dispersed by aspiration through a siliconized Pasteur pipette after 30 minutes of digestion.

After initial tissue digestion, most stromal cells were separated from large epithelial clumps by filtration through two nylon membrane filters (105 and 88 μm, respectively). Retained epithelial clumps were washed in Hank's balanced salt solution (pH 7.4) by centrifugation (400 *g*) before further enzymatic digestion in Hank's balanced salt solution containing 0.5% collagenase, 0.1% hyaluronidase, 0.1% pronase, 0.02% deoxyribonuclease, and 2% chicken serum. Subsequent to the second enzymatic digestion clumps of epithelial cells were collected on an 88 μm nylon mesh filter (allowing contaminating stromal cells to pass), washed twice, and resuspended in 2 ml DME/F-12/FBS. This suspension was layered over 10 ml of DME/F-12/FBS in a 15 ml conical tube for a 30-minute unit gravity sedimentation at 37° C. This step was repeated with only the bottom 2 ml of cells from the first sedimentation.

Final purification of epithelial cells was achieved by allowing rapid selective adherence of the few remaining stromal cells to 25 cm^2 tissue culture flasks. Epithelial clumps were suspended in DME/F-12/FBS and plated for 30 minutes at 37° C in a humidified environment with 5% carbon dioxide. The nonattached epithelial cells were collected and the procedure was repeated once. Epithelial cell viability was ascertained in a 0.04% solution of trypan blue in phosphate-buffered saline solution (pH 7.2), and an estimate of cell numbers within each cell preparation was determined with a hemocytometer.

Epithelial cell cultures. For routine assessment of culture purity, epithelial cells were cultured for 2 to 3 days as a monolayer on Thermanox tissue culture disks (Miles Laboratories, Naperville, Ill.) placed in four-well culture plates. These cells were evaluated morphologically and with an immunohistochemical probe for the epithelial cell-specific intermediate filament, cytokeratin, as previously described.[9] Otherwise, purified epithelial cells were cultured in Millicell-CM tissue culture plate inserts (Millipore Products Division, Bedford, Mass.) coated with a layer of Matrigel biomatrix (Collaborative Research, Boston, Mass.). Between 1 to 5×10^5 cells/insert were seeded and allowed to attach in DME/F-12/FBS for 48 to 72 hours. Subsequently, cultures were maintained up to 12 days in serum-free DME/F-12 medium supplemented with insulin, transferrin, selenium, bovine serum albumin, and linoleic acid (ITS$^+$; Collaborative Research, Boston). On termination, inserts containing cells cultured on biomatrix were washed in ice-cold phosphate-buffered saline solution and fixed in 4% buffered formalin. Subsequently, the support membranes with attached epithelial cells were carefully removed from inserts with a scalpel and embedded in paraffin for localization of cellular TAG-72 epitope by monoclonal antibody B72.3 immunoreactivity.

Immunohistochemistry. The cytokeratin monoclonal antibody PKKI, directed against a 40 to 60 kd cytoskeletal fraction from pig kidney epithelial cells was purchased from Labsystems (Morton Grove, Ill.). Monoclonal antibody B72.3 used for this study was generated in the laboratory of Dr. Jeffrey Schlom (National Cancer Institute Section on Tumor Immunology, Bethesda, Md.).[1-5] Immunolocalizations of TAG-72 epitope or cytokeratin were accomplished with the avidin-biotin complex technique,[11] with streptavidin to lower background staining. As a negative control, an identical isotype antibody (monoclonal antibody MOPC-21; Litton Bionetics, Charleston, S.C.) was used under the same conditions.

Sections from paraffin-embedded biopsy specimens or cells grown on biomatrix were pretreated with heat-inactivated horse serum, washed in phosphate-buffered saline solution, and exposed to primary antibody (1:100 in phosphate-buffered saline solution containing 1% horse serum) for 1 hour at room temperature. Specimens then were washed and incubated with biotinylated secondary antibody (horse antimouse immunoglobulin G) for 1 hour. After further washing, tissues were exposed to streptavidin-biotin-peroxidase complex for 1 hour and reactivity was visualized with diaminobenzidine. All specimens were counterstained with Gill's hematoxylin and examined by light micros-

copy. Immunoreactivity was considered positive when a distinct, brown, granular diaminobenzidine precipitate was evident.

Results

Immunoreactivity of endometrial biopsy specimens to monoclonal antibody B72.3. No sample (n = 7) of intact endometrium obtained during the proliferative interval of the menstrual cycle intially showed monoclonal antibody B72.3 immunoreactivity in any region of the tissue (Fig. 1, *A*). Conversely, all (n = 9) biopsy specimens obtained during the secretory menstrual interval showed immunoreactivity to monoclonal antibody B72.3 in glandular epithelium and, to a lesser extent, luminal surface epithelial cells (Fig. 1, *B*). Considerable heterogeneity of TAG-72 epitope expression was noted between luminally situated glands (strongest reactivity) and basal glands (no reactivity). Furthermore, some cellular heterogeneity was observed among adjacent luminal glands such that the number of immunoreactive cells among the luminal glands ranged from approximately 10% to >30%. Immunoreactive material was often noted in the lumen of reactive glands.

Isolation and assessment of endometrial epithelium. The yield of purified epithelium from the portion of biopsy material available for study did not vary appreciably in relation to either patient age or menstrual interval and consistently ranged between 10 to 15 × 10^6 cells. Cell viability after purification procedures was routinely >90%. Thus a minimum of 10 culture replicates could be established from each biopsy sample. Epithelial cells cultured on Thermanox tissue culture disks assumed a flattened, whorled configuration after 3 to 4 days, and the purity of these cell populations was assessed by cytoplasmic immunoreactivity to anticytokeratin antibody. Consistent with previous observations,[9] contamination of epithelial cell preparations by stromal or endothelial cells was <5%.

Immunoreactivity of cultured epithelium to monoclonal antibody B72.3. A uniform monolayer of cuboidal cells was evident after 5 to 6 days of culture on biomatrix, in contrast to the flattened morphology of epithelial cells cultured on plastic. Cells cultured on biomatrix maintained a polar cellular architecture that is characteristic of in vivo epithelium. No overt differences in cellular morphology could be detected by phase microscopy between cells from biopsy specimens obtained during the proliferative versus the secretory menstrual interval.

After 4 to 6 days of serum-free culture on biomatrix, strong immunoreactivity with monoclonal antibody B72.3 was shown in cells obtained during the secretory interval (Fig. 1, *C*). Such immunoreactivity was maintained for up to 12 days, at which point cultures were terminated. Unexpectedly, a similar pattern of monoclonal antibody B72.3 immunoreactivity was observed in epithelial cells isolated from proliferative interval biopsy specimens by 8 days of serum-free culture on biomatrix (Fig. 1, *D*), which was also maintained until cultures were terminated.

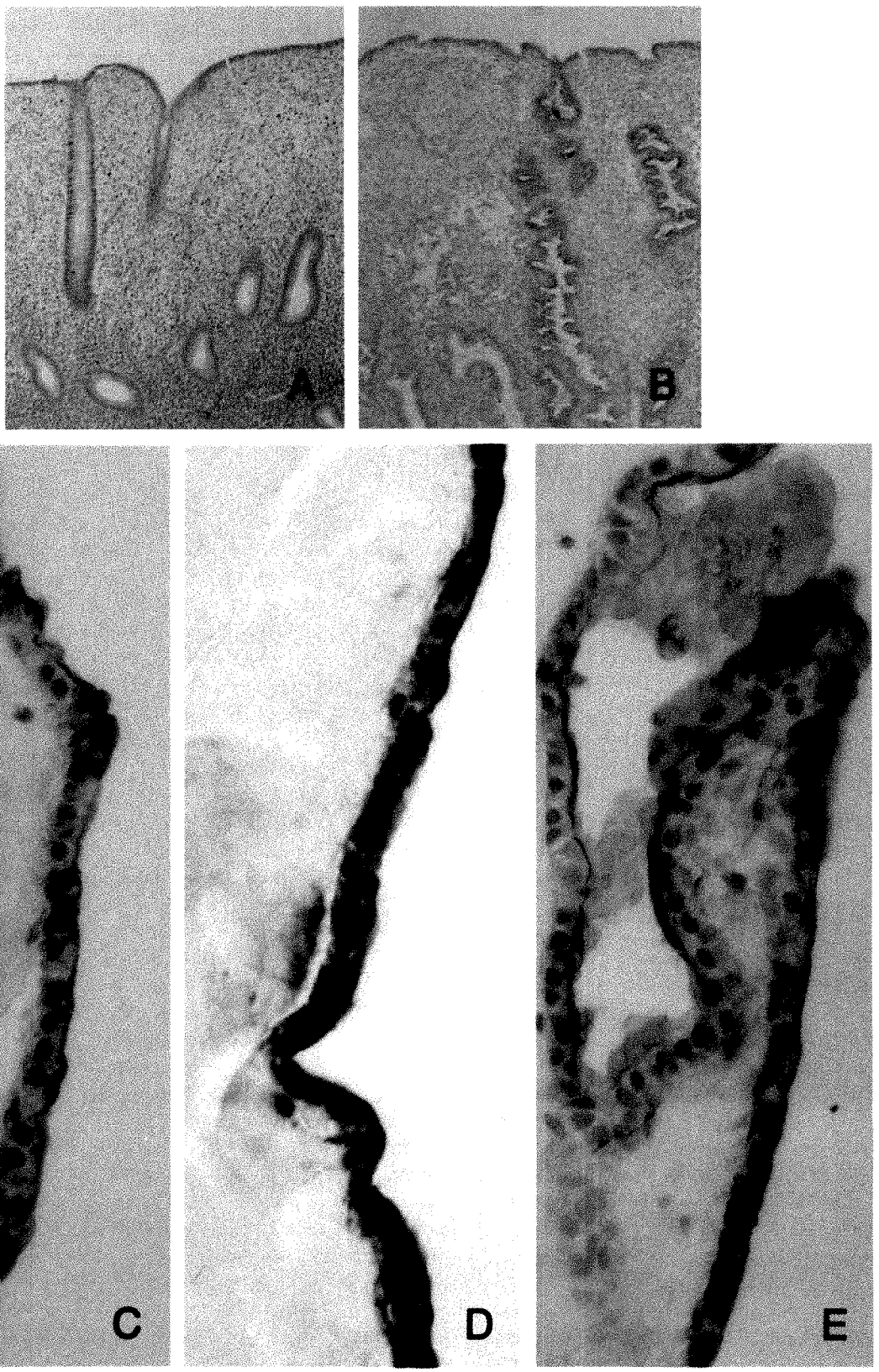
Cells cultured on a thin layer of biomatrix generally appeared to form a continuous polar monolayer. However, near the edge of culture plate inserts where a meniscus effect produces a slightly thicker biomatrix bed, some epithelial cells appeared to organize into folded gland-like structures (Fig. 1, *E*). These "glands" were present in cultures of epithelial cells obtained during both proliferative and secretory intervals, and closely resembled in vivo glandular architecture. The apical surface of cells forming these structures was found to be highly immunoreactive to monoclonal antibody B72.3, and immunoreactive material was often present within the "lumen" as well.

Comment

Our observations of monoclonal antibody B72.3 immunoreactivity in glandular epithelium of normal secretory interval endometrium is consistent with those previously reported,[5] but the physiologic significance of TAG-72 epitope expression remains unknown. It also remains unclear whether such immunoreactivity reflects expression of the same molecule elaborated by tumor cells (TAG-72), or whether an identical or similar epitope is an integral component of an otherwise unrelated molecule.

The possibility exists that monoclonal antibody B72.3 recognition of secretory endometrium may bear a coincidental relationship to the expression of this epitope in tumors. Monoclonal antibodies directed against specific epitopes have been shown to cross-react with other antigenic determinants with enough structural similarity to allow recognition,[12] and often with apparently unrelated antigens.[13] For example, monoclonal antibodies raised against insulin and growth hormone recognize tissues in which those genes are not expressed.[14] This unexpected multiple organ reactivity is a widely recognized phenomenon rarely observed with polyclonal antisera.

Recent research has emphasized the importance of polarity in cell functions such as endocytosis and exocytosis, molecular sorting, epithelial transport, and hormonal responsiveness.[15-17] Culture of epithelial cells on porous substrates has been shown to allow establishment of polarity in vitro, thus permitting a more "in vivo-like" performance of normal cellular functions.[17] As such, our observations that epithelial cells obtained from secretory interval endometrium continued to express the TAG-72 epitope in culture, when grown as a polarized monolayer on biomatrix, were


A
B
C
D
E

consistent with descriptions of LS-174T colon cancer cell growth on plastic versus agar gels,[8] and confirmed our predictions.

We were surprised to find that, unlike the in vivo situation, endometrial epithelial cells obtained during the proliferative interval developed and maintained TAG-72 epitope expression after a short period in culture. This could be explained by the absence in vitro of one or more inhibitory factors, possibly of stromal origin, which are normally present during the proliferative interval in vivo. This notion is supported by descriptions of stromal regulation of epithelial cell function[18, 19] and a report of stromal-epithelial connections in the normal human endometrium.[20] Alternatively, the Matrigel biomatrix used in this study may contain factors that stimulate (or permit) glandular epithelial differentiation resulting in TAG-72 epitope expression. In this context, our observation that epithelial cells began to form apparent gland-like structures, when the thickness of the biomatrix permitted, may indicate that Matrigel components are directing or permitting some epithelial cell differentiated functions in vitro.

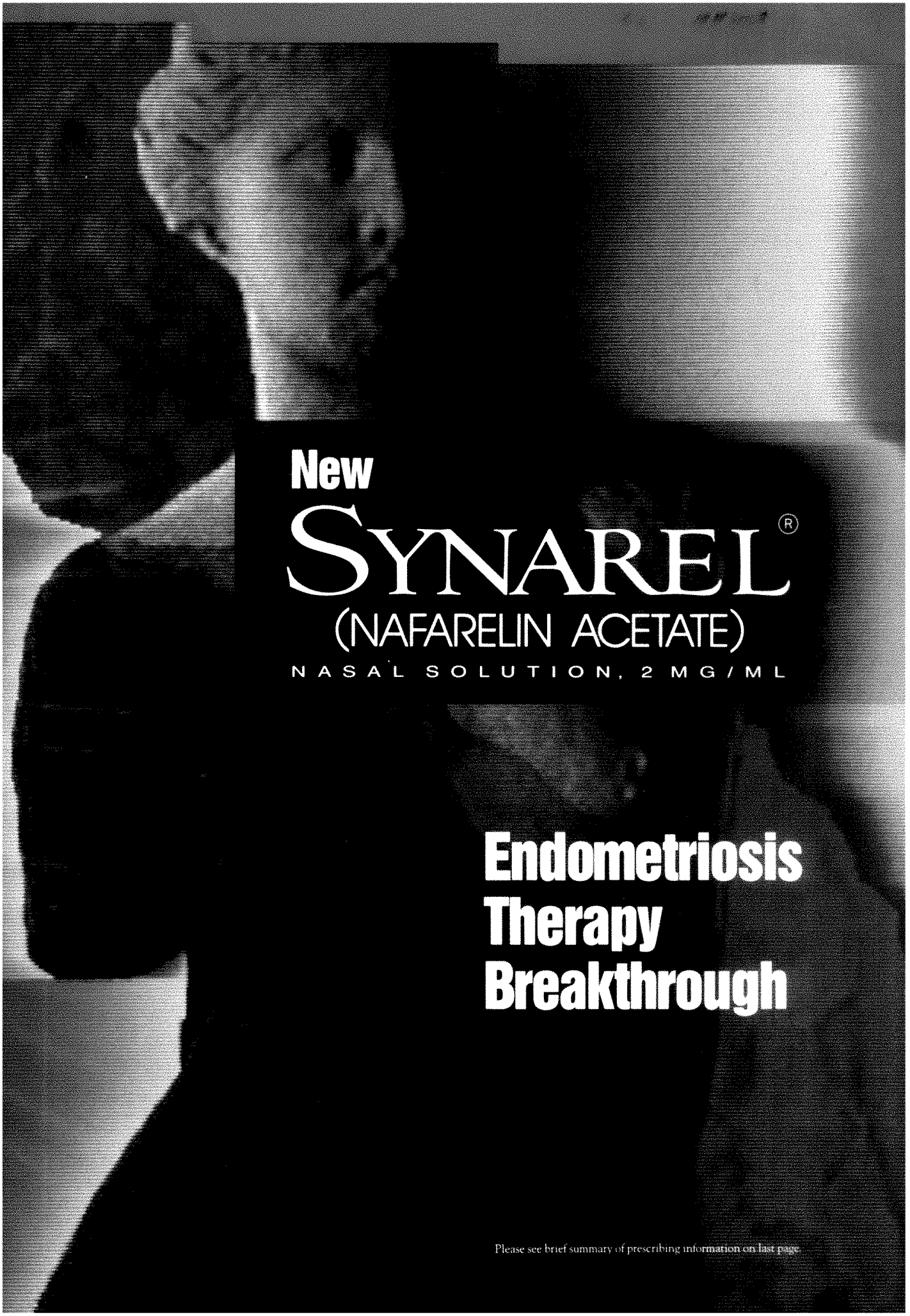
Normal endometrial epithelial cells cultured under the conditions described here exhibit monoclonal antibody B72.3 reactivity in vitro at a level consistent with that observed in vivo. Furthermore, in contrast to the marked heterogeneity of TAG-72 expression observed in vivo, cultures of endometrial epithelium on biomatrix exhibited almost uniform expression among all cells observed after 6 to 8 days of culture. Thus we believe that TAG-72 epitope expression by endometrial epithelial cells in vitro may prove to be a reliable marker for the study of factors that regulate endometrial maturation. This model could provide important information on the role of extracellular matrix and stromal components in modulating cellular differentiation in this dynamic tissue. Furthermore, understanding the regulation of TAG-72 epitope expression in the endometrium may provide insight into its regulation in neoplastic tissues.

The technical support of Vernon Summerlin, Lynne Black, and Mary Stevenson is gratefully acknowledged. We also thank Drs. Jeffrey Schlom and Barbara Vonderhaar for editorial comments.

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Fig. 1. Glandular epithelium in section of formalin-fixed intact human endometrium obtained during proliferative **(A)** and secretory **(B)** intervals of menstrual cycle. No monoclonal antibody B72.3 immunoreactivity is noted in proliferative interval tissue, whereas intense immunoreactivity is noted in glandular and luminal epithelium of secretory interval tissue. Epithelial cells purified from endometrium obtained during proliferative **(C)** and secretory **(D)** intervals of normal menstrual cycle, and grown on Matrigel biomatrix for 8 days exhibit equally intense monoclonal antibody B72.3 immunoreactivity. Epithelial cells cultured in areas of biomatrix where gel coating was thickest formed immunopositive gland-like structures **(E)**, reminiscient of in vivo glands. (**A** and **B,** final magnification ×78; **C, D,** and **E,** final magnification ×520.)


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The intrauterine sound environment of the human fetus during labor

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Ten pregnant women near term with medical indications for internal monitoring during labor were studied to quantify the intrauterine sound environment. The intrauterine background noise was measured with a miniaturized hydrophone placed transcervically at the level of the fetal neck under ultrasonographic guidance. In eight women no cardiovascular noise was audible and the intrauterine noise consisted predominantly of low-frequency noise (<100 Hz) from 60 to 85 dB. Above 100 Hz, the sound pressure level was <60 dB, decreasing to 40 dB above 500 Hz. In only two women maternal cardiovascular sounds were audible during uterine relaxation and disappeared during uterine contraction. Maternal bowel sounds and maternal vocalization were well above the intrauterine background noise. Because of this relative quietness, we hypothesized that the fetal acoustic environment could be altered significantly during antenatal vibratory acoustic stimulation. (Am J Obstet Gynecol 1990;163:484-90.)

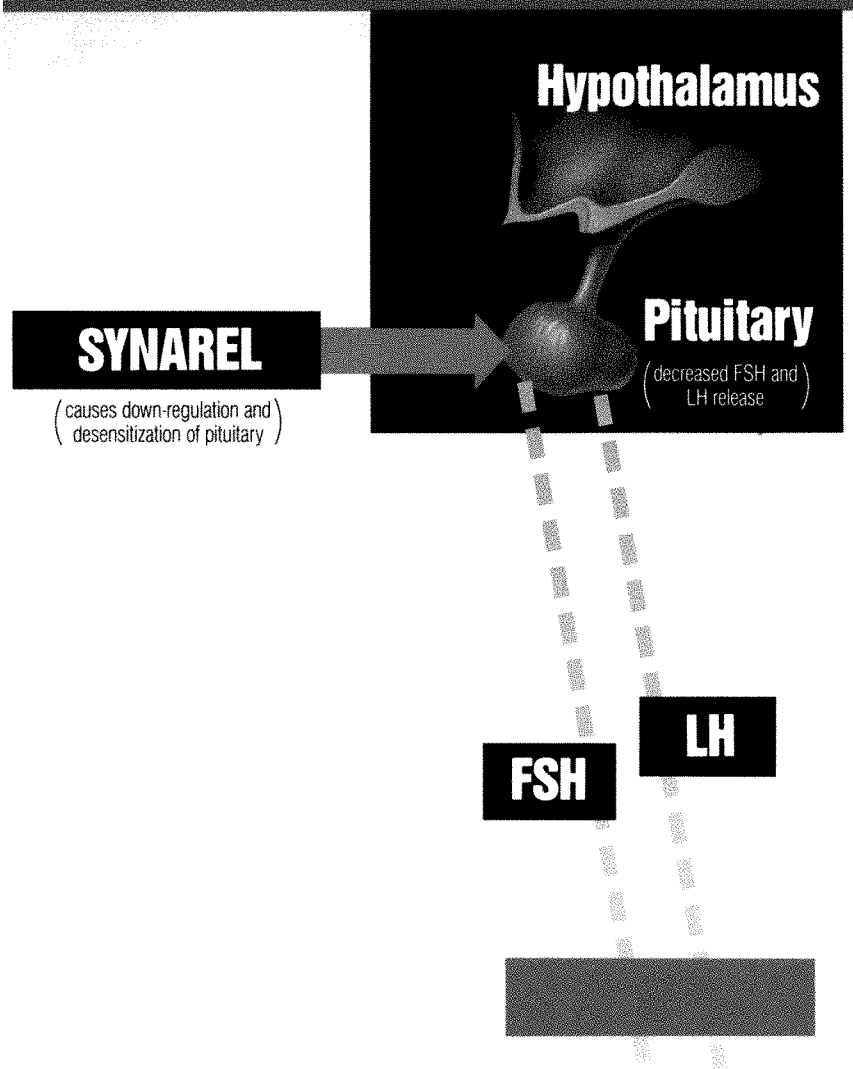
Key words: Fetal sound environment; effect of uterine contraction on intrauterine background noise; vibratory acoustic stimulation

In humans the fetal sound environment is believed to consist of loud pulsations from the maternal cardiovascular system, possibly from the main arteries and the placenta.[1,2] The overall sound pressure level in the pregnant human uterus has been reported to be as high as 95 dB.[1] More recently, in the chronically prepared pregnant ewe, the intrauterine background noise has been reported to be approximately 60 to 87 dB and increased by specific activities of the animal such as drinking.[3,4] Because of the increasing interest in the use of external vibratory acoustic stimulation in the assessment of fetal health,[5] it is important to determine the fetal sound environment under basal conditions. The purposes of this study were to quantify, in a group of pregnant women at term, the intrauterine sound environment during the active phase of labor and to determine the effect of uterine activity on the intrauterine background noise.

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**Medical Research Council of Canada scholar.*
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Patients and methods

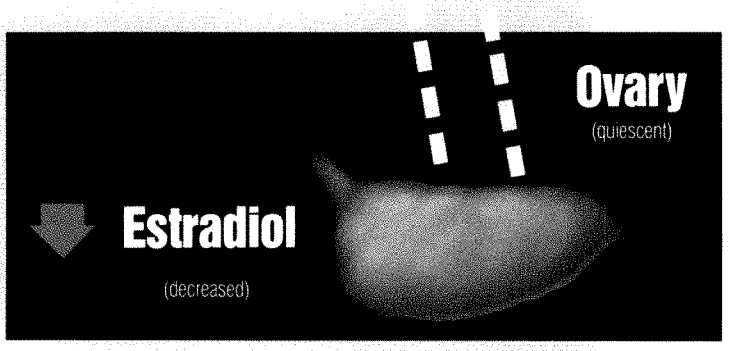
Patients. Informed consent was obtained from 10 pregnant women between 37 and 42 weeks' gestational age (Table I). All women had medical indication(s) for internal monitoring (intrauterine pressure catheter and fetal scalp electrode for fetal heart rate tracing) during labor as illustrated in Table II. Six women had been placed under epidural anesthesia before the experi-



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ment and four were unmedicated at the time the study was performed. All fetuses were singleton and in a vertex presentation at the time of delivery.

Experimental design. All studies began during the active phase of labor (>3 cm cervical dilatation; range 3 to 8 cm), after rupture of membranes, with patients resting in a recumbent position with a slight tilt to the left. After insertion of the fetal scalp electrode, an intrauterine pressure catheter (posteriorly to the fetal head) and a miniaturized hydrophone (anteriorly to the fetal head), the following measurements were obtained. A sound pressure level meter (model 2205, Bruel and Kjaer, Copenhagen) was used to record ambient overall sound pressure level in the labor room, at 1 cm from the surface of the maternal abdomen. Intrauterine background noise was measured during the peak of three uterine contractions and during three periods of uterine relaxation. The average of these three measurements was used to determine the sound pressure level spectrum for each patient during the two states of uterine contractility. Headphones also were used to listen to intrauterine sounds simultaneously as they were being recorded to identify any that were audible. After these baseline measurements, women were asked to pronounce *99* during uterine relaxation, to determine if maternal vocalization could be transmitted inside the uterine cavity. Instantaneous sound pressure level spectra were then obtained and stored for off-line analysis on floppy disks.

Measurements of intrauterine sound pressure levels. A real-time ultrasonographic scanner (model SAL-30A, Toshiba Corp., Shimoishi, Japan; 3.5 MHz transducer) was used to confirm the fetal presentation, the location of the fetal neck and the placenta, and the maternal abdominal wall thickness (maternal soft tissue thickness plus anterior uterine wall thickness). After insertion of the intrauterine pressure catheter and fetal scalp electrode, a custom-built miniaturized hydrophone (model No. 1, Sparton of Canada Ltd., London, Ontario) fitted to the end of a No. 16 polyvinyl nasogastric tube was inserted transcervically to the level of the fetal neck. The catheter was placed anteriorly to the fetal head in eight women and favored a slightly lateral position in two. In all women the hydrophone was placed above the fetal head at the level of the fetal neck and was in a pocket of amniotic fluid. Direct ultrasonographic visualization of the stainless steel body of the hydrophone (width of 9.5 mm) and turbulent flow produced around the hydrophone head by rapid infusion of sterile water into the nasogastric tube were used to confirm location of the miniaturized hydrophone.

The hydrophone was 19.1 mm long and 9.5 mm in diameter, with a flat frequency response from 400 Hz to 20 kHz (±2 dB). Below 400 Hz, the hydrophone sensitivity decreased by 5 dB at 300 Hz, 8 dB at 200 Hz, and 13 dB at 100 Hz, to a maximum of 23 dB at 10 Hz (sensitivity expressed as decibels per volt per 20 μPa). Therefore below 400 Hz sound pressure levels were corrected by means of specific sensitivity curves before final analysis. The electrical noise floor (decibels per 20 μPa per $\sqrt{\text{hertz}}$), which is the minimum sound pressure level that could be detected by the hydrophone, was 30 dB from 200 Hz to 15 kHz with a progressive rise to 33 dB at 100 Hz and a maximum of 55 dB at 10 Hz (as per calibration by Sparton of Canada). In comparison, the human ear can detect sound pressure level >30 dB at frequencies between 30 and 20,000 Hz.

Table I. Patient characteristics

	Mean ± SEM	Range
Gestational age at test (wk)	[illegible] ± 0.5	37-42
Birth weight (gm)	[illegible] ± 135	3025-3910
5 min Apgar score	[illegible] ± 0.1	7-10
Umbilical artery pH at birth (n = 9)	[illegible] ± 0.01	7.20-7.35
Primigravid	5	

Table II. Primary indications for internal monitoring

Primary indication	*No. of patients*
Oxytocin stimulation	3
Meconium	2
Pregnancy-induced hypertension	2
Previous cesarean section	2
Postdates (>42 wk)	1

The signal cable attached to the stainless steel body of the hydrophone was threaded through the lumen of the nasogastric tube and connected to a battery-powered preamplifier (Sparton of Canada). The output from the preamplifier was interfaced with an isolation line audiotransformer (model 195850G, Hammond, Willowdale, Ontario), and the output signal was processed by a real-time computer-based two-channel frequency analyzer (model 2630, Tektronix, Campbell, Calif.) and stored on floppy disks for off-line analysis. Calibrations of the hydrophone were done with electronically generated sounds of 94 and 114 dB (2×10^{-5} N/m^2) at 1 kHz (Department of Mechanical Engineering, University of Western Ontario) to determine a reference point for absolute sound pressure levels before and after each experiment. Fast Fourier Transform was done with a Hanning window, 1 kHz bandwidth, 1024 points, at a sampling rate of 2.56 kHz.

The average of 20 sound pressure level spectra for baseline intrauterine background noise and the average of two spectra during maternal vocalization were used to define one spectrum. The miniaturized hydrophone coupled with the preamplifier, the audio-transformer,

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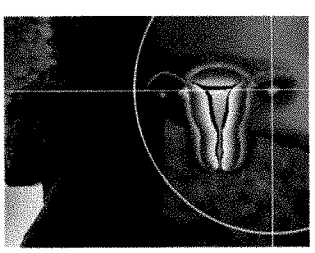
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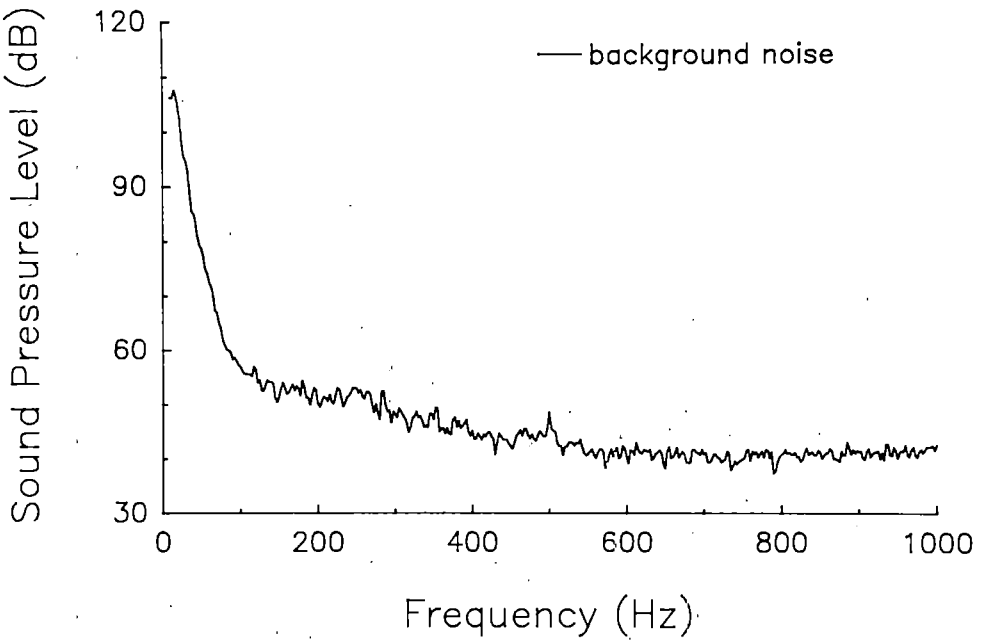


Fig. 1. Typical example of intrauterine background noise recorded at level of fetal neck (2×10^{-5} N/m^2.

and the frequency analyzer were approved by the Canadian Standards Association for electrical safety as class risk III.[6] These standards are the same as for electronic internal fetal heart rate monitoring during labor and included: (1) a maximum allowable current leakage of <20 μA at patient-applied part regarded as source (5 μA for the hydrophone) and (2) a minimum dielectric strength test voltage at 60 Hz of 2500 V source for 1 minute, between accessible non-current-carrying metal parts and metal foil wrapped around the power supply cord at the point of entry in the housing.[6]

Fetal heart rate and uterine contractions were continuously recorded throughout the experiments on a Hewlett Packard 8040A (Hewlett Packard GMBH, Boeblinger, Federal Republic of Germany) cardiotocograph. At the end of each study, the hydrophone with the nasogastric tube was removed without any difficulty.

Data analysis. The overall ambient background noise (decibels) in the room was determined at the onset of each experiment. The absolute sound pressure level (decibels); 2×10^{-5} N/m^2) for each intrauterine sound spectrum obtained was determined automatically in 12.5 Hz increments from 12.5 Hz up to 1000 Hz, and the mean value was reported. All results are presented as means ± SEMs for each frequency. Statistical significance to examine the effect of frequency, uterine contractions, parity, epidural anesthesia, and placental location on sound pressure levels was determined by analysis of variance with repeated measures.

Results

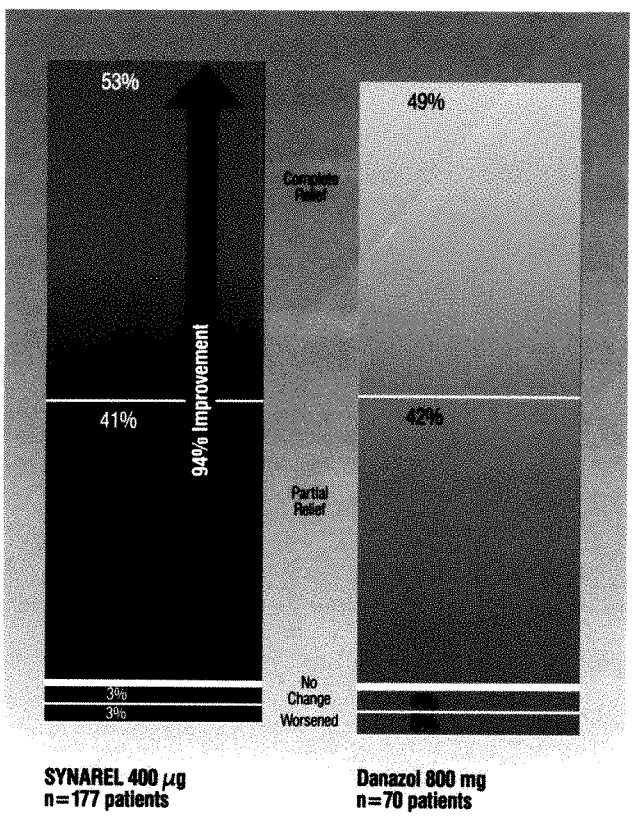
Maternal cardiovascular sounds. The mean overall ambient noise as measured at 1 cm from the maternal abdomen was 55.9 ± 1.6 dBA (range 49 to 64 dBA). The frequency spectrum of the ambient noise consisted of low-frequency noise of 57 dB at 12.5 Hz decreasing to 40 dB at 60 Hz and 32 dB above 100 Hz. The mean maternal abdominal wall thickness was 3.1 ± 0.2 cm (range 2.3 to 4.5).

Fig. 1 shows a typical example of the intrauterine background noise during uterine relaxation. In eight out of 10 women, maternal cardiovascular sounds were not audible during uterine relaxation. The mean absolute sound pressure level was 97.4 ± 1.8 dB at 12.5 Hz, decreasing significantly to 59.2 ± 2.5 dB at 100 Hz, 48.4 ± 1.3 dB at 500 Hz, and 43.3 ± 0.4 dB at 1000 Hz (analysis of variance, $p < 0.001$) (Fig. 2). There was no significant difference in absolute sound pressure levels at any frequency between uterine relaxation and uterine contraction (Fig. 2).

In two women maternal cardiovascular sounds were clearly audible. The absolute sound pressure level during uterine relaxation in these two women was 19 dB higher at 100 Hz than in the eight women without audible cardiovascular sounds (78 and 59 dB, respectively, Fig. 3). At 650 Hz the difference in sound pressure level was only 2 dB. Below 100 Hz and above 650 Hz there was no difference in absolute sound pressure level between the two groups (Fig. 3). During uterine contractions, maternal cardiovascular sounds were no longer audible in these two women and the intrauterine

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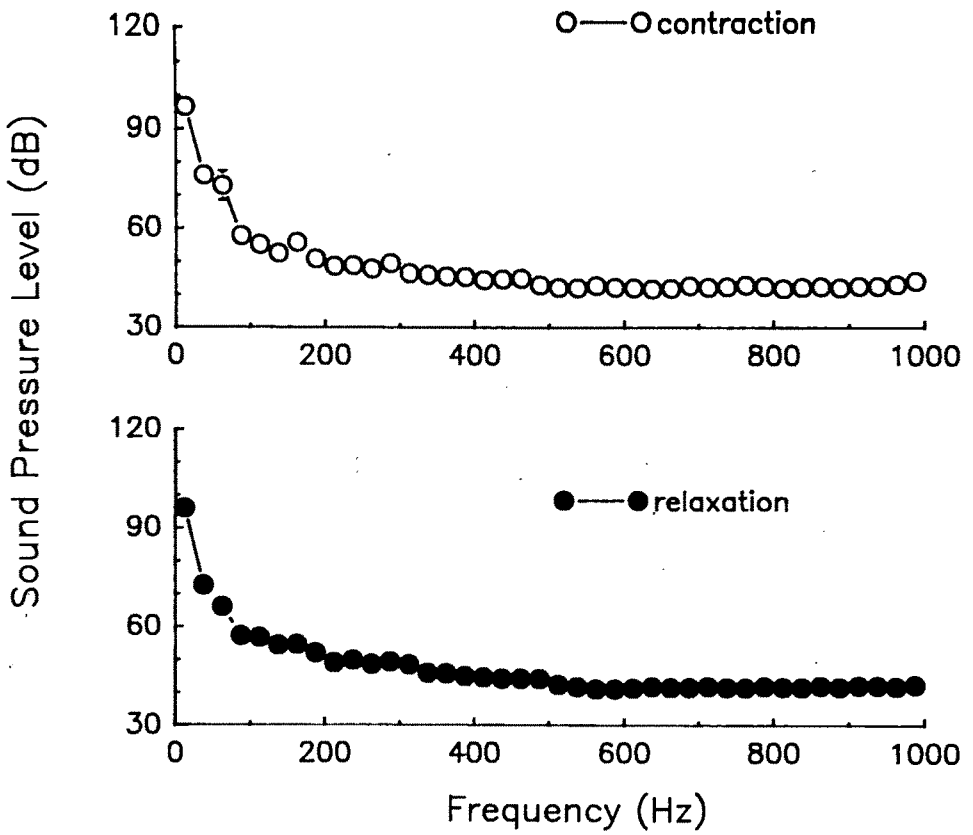


Fig. 2. Mean absolute sound pressure level (decibels; 2×10^{-5} N/m^2) (±SEM) was plotted in 12.5 Hz increments up to 1000 Hz during uterine contraction *(top)* and during uterine relaxation *(bottom)*. *Symbols* are larger than SEM.

background noise was similar to that of the eight women without audible intrauterine vascular sounds (Fig. 3).

No significant difference was demonstrated in intrauterine sound pressure levels for primiparous women (n = 5) versus multiparous women (n = 5), for anterior placentas (n = 4) versus other locations (n = 6), and for women with epidural anesthesia (n = 6) versus those without medication (n = 4), in states of both uterine relaxation and uterine contraction.

Maternal bowel sounds and vocalization. In three women bowel sounds were audible during the experiment and were recorded simultaneously (Fig. 4). They consisted of two different qualitative types: one was a "low-pitched," "rumbling" sound (Fig. 4, top) and one was a "high-pitched," "tinkling" sound (Fig. 4, bottom). The sound spectrum was characterized by varying intensities between 40 and 60 dB at frequencies above 200 Hz. The same patterns of bowel sounds were seen in the three women studied.

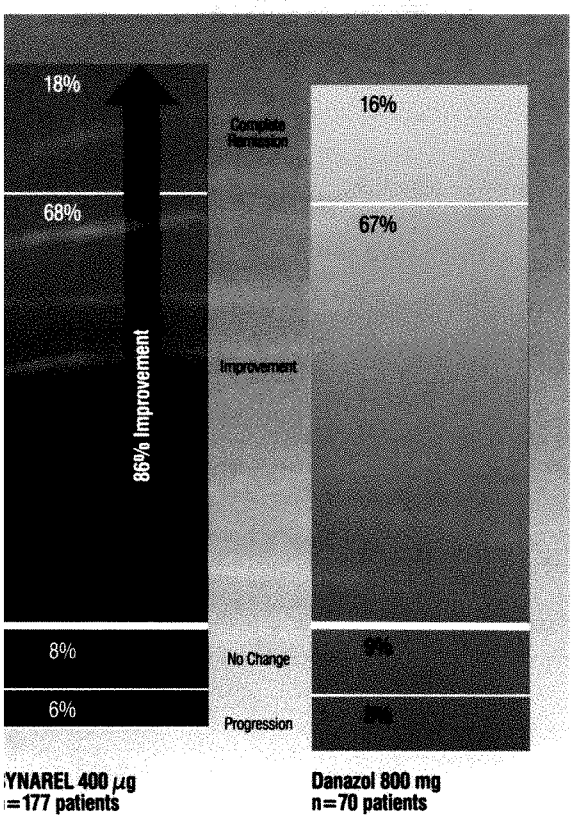
Maternal vocalization was easily recorded in utero in the 10 women. The sound spectrum produced by pronouncing *99* was characterized by peak intensities of 70 to 75 dB at 200 to 250 Hz (which is the range of a normal female voice) and was approximately 20 dB above the intrauterine background noise at those frequencies (Fig. 5). A similar spectrum of sound was seen in all women during vocalization. The term *99*, as pronounced by the mother, was slightly muffled but clearly audible above the background noise.

Comment

The results indicated that the intrauterine sound environment of the human fetus during active labor predominantly consisted of low-frequency noise (<100 Hz) from 60 to 85 dB. Above 100 Hz the sound pressure level was <60 dB decreasing to 40 dB above 500 Hz. In our experimental conditions maternal cardiovascular sounds usually were not audible. Maternal bowel sounds and vocalization were well above the intrauterine background noise.

Many investigators have reported that maternal heart sounds in humans dominate the intrauterine sound environment and could contribute to fetal imprinting.[1, 2, 7] However, maternal cardiovascular sounds are not consistently detected from recordings of intrauterine background noise of pregnant ewes.[3, 4, 8, 9] Our data indicated that maternal vascular noise was clearly

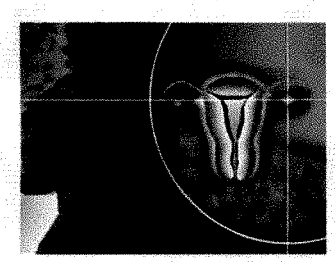
5% Of Patients
lowed Improvement Of
ndometriotic Lesions



nges in laparoscopy scores from admission to
of therapy

- Post-therapy laparoscopy confirmed improvement in all stages† of endometriosis
- Number of patients in Stages III and IV decreased 42% and 57% respectively
- Retreatment cannot be recommended since safety data for retreatment are not available

†Based on American Fertility Society laparoscopy score stages: 0 (absent, score 0), I (minimal, 1–5), II (mild, 6–15), III (moderate, 16–40), IV (severe, >40).



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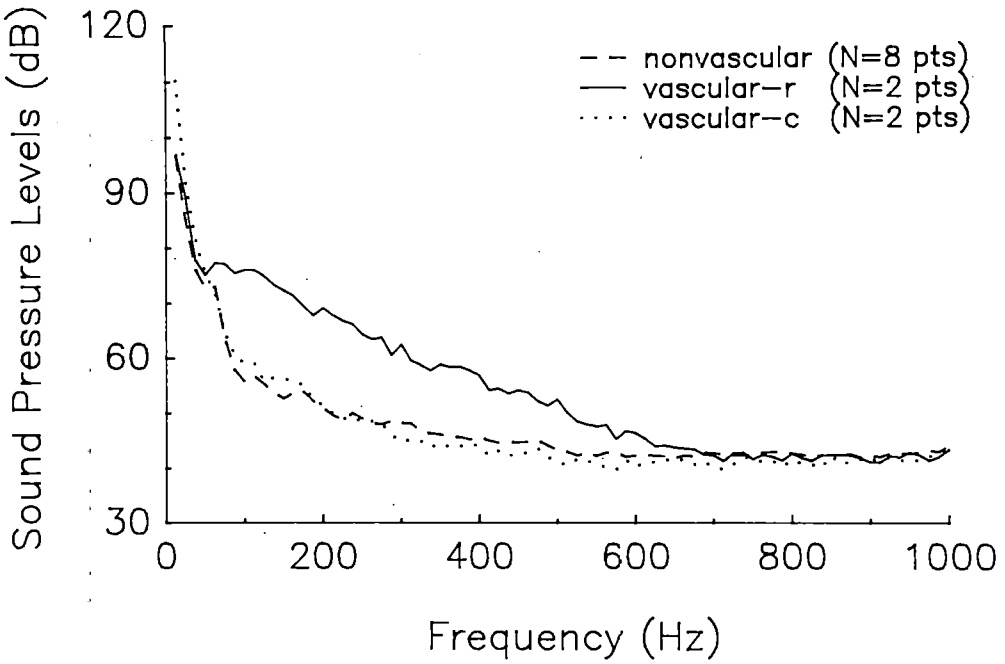


Fig. 3. Mean absolute sound pressure level (decibels; 2×10^{-5} N/m^2) was plotted in 12.5 Hz increments up to 1000 Hz in eight women in whom there were no audible maternal vascular sounds during uterine relaxation *(dashed line)*. Mean absolute sound pressure level (decibels) in two women, at which time vascular sounds were audible during uterine relaxation *(solid line)* but were not audible during uterine contraction *(dotted line)*, are plotted on same frequency scale.

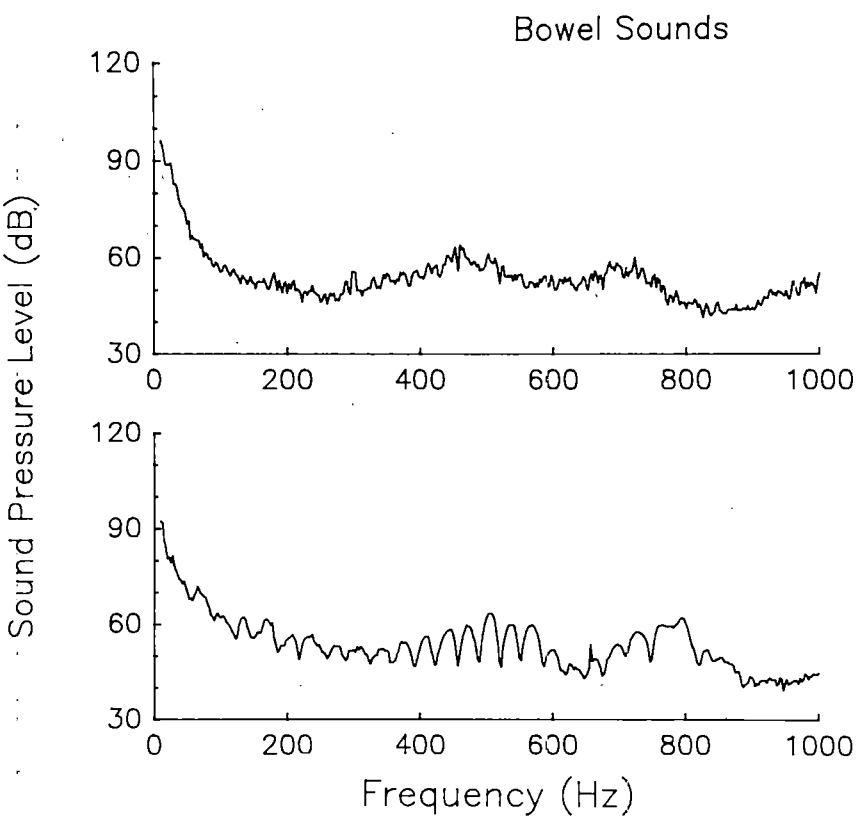
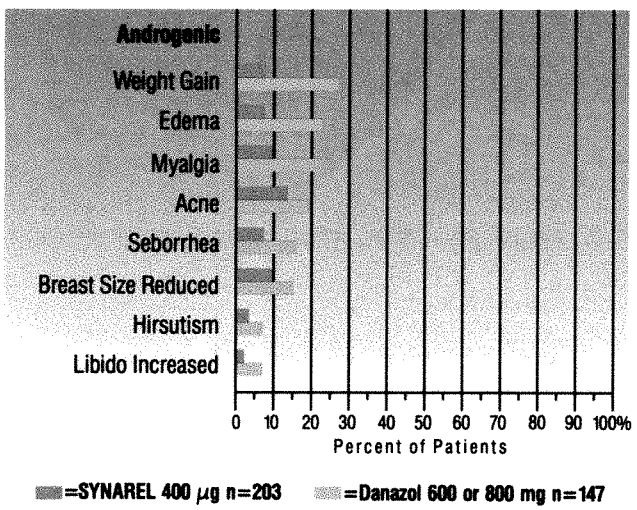


Fig. 4. Typical example of intrauterine background noise recorded during audible low-pitched *(upper)* and high-pitched *(lower)* bowel sounds (2×10^{-5} N/m^2).

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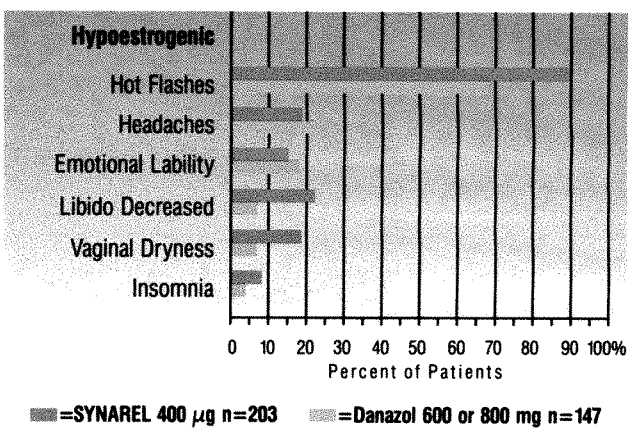
Synarel Exhibits Fewer Masculinizing Side Effects Than Danazol



Adverse events during 6 months treatment

- More frequent and/or severe with danazol:
  Weight gain
  Edema
  Acne
  Oily skin
  Hirsutism
- Some androgenic effects of danazol—such as voice deepening—may be irreversible[3]
- Patients should be advised to use non-hormonal methods of contraception when taking SYNAREL

Synarel Exhibits Predictable Hypoestrogenic Profile



Adverse events during 6 months treatment

- Estrogen levels return to normal after cessation of therapy
- Bone changes largely reversible 6 months post-treatment

Bone Density Changes During And After Treatment With SYNAREL (400 μg/day)

Site Method Units	Time of Study Baseline	End of Treatment	Post-treatment
Lumbar Vertebrae QCT,* Integral (g/vertebrae) n=21	13.4	12.8 −4.3%	13.1 −3.3%
Trabecular Bone of Vertebrae QCT* (mg/cc) n=23	161.3	147.6 −8.7%	152.0 −4.9%
Lumbar Vertebrae DPA† (g/cm^2) n=6	0.98	0.93 −5.9%	0.96 −1.4%
Distal Radius SPA** (Units) n=6	40.2	39.5 −1.6%	39.6 −0.8%

Percent changes from baseline

*Quantitative computed tomography
†Dual photon absorptiometry
**Single photon absorptiometry

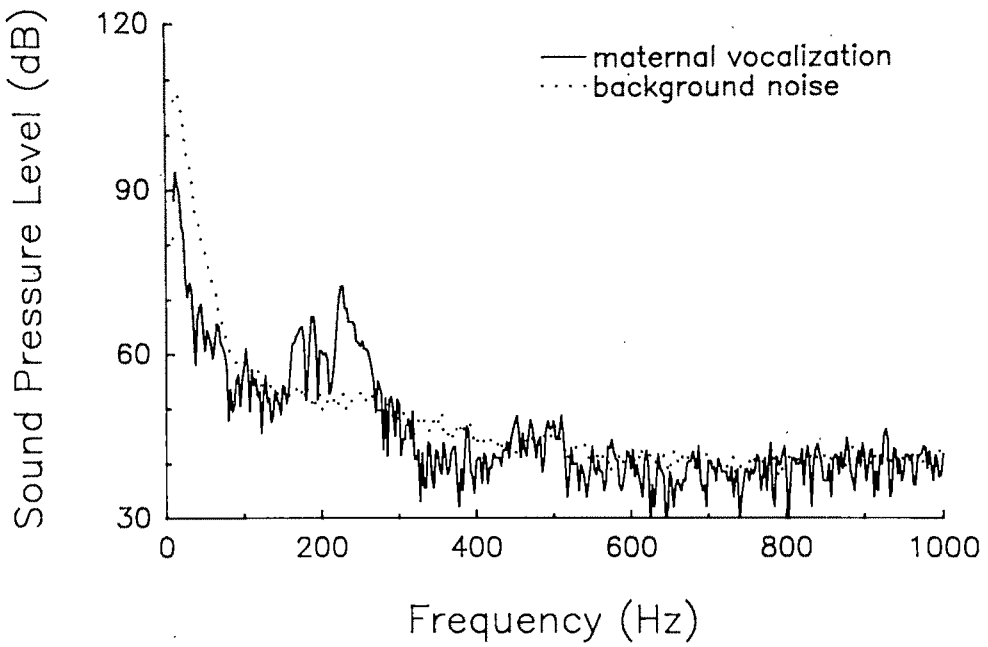


Fig. 5. Typical example of instantaneous intrauterine background noise during maternal vocalization *(solid line)* superimposed on average intrauterine background noise under basal conditions *(dotted line)* (2×10^{-5} N/m^2).

audible in only two out of 10 patients during uterine relaxation and disappeared during uterine contraction, suggesting that the hydrophone was sensing blood flow in the uteroplacental circulation, which is known to decrease during uterine contractions in labor.[10]

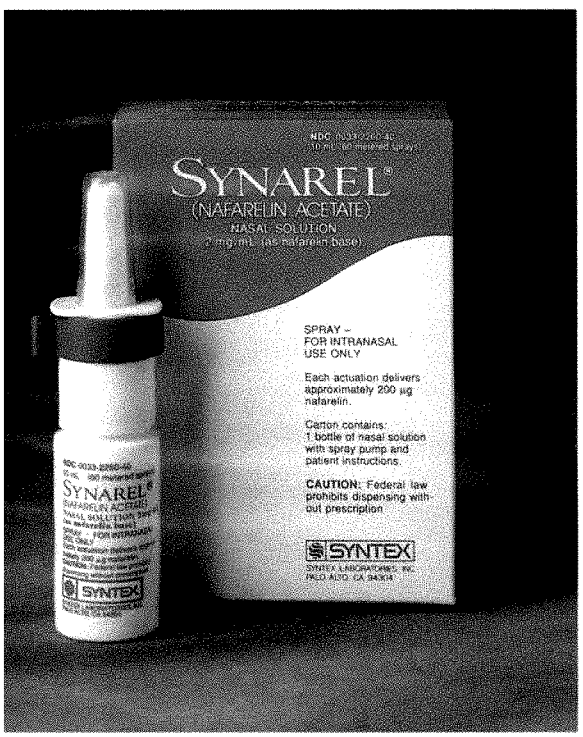
Using ultrasonographic guidance, we have been able to insert a miniaturized hydrophone anteriorly, at the level of the fetal neck, which is a location similar to that previously described in the pregnant ewe to record intrauterine background noise.[3] This technique contrasted with other human studies during which a microphone covered with a rubber sleeve was inserted either inside the vagina,[11] inside the cervix,[1] or posteriorly close to the maternal aorta.[12] These three anatomic regions are known to be well vascularized during pregnancy and could have contributed to the assumption that the intrauterine sound environment consisted mainly of loud vascular pulsations during human pregnancy.[1, 12]

The low-frequency component of the intrauterine background noise (<100 Hz) has been reported by Querleu et al.[12] in humans and by Vince et al.[3, 4] and more recently by Gerhardt et al.[9] in the pregnant ewe. Although it was believed to be due to maternal vascular sounds in humans,[2] it has also been measured after death of pregnant ewes.[9] It is possible that this low-frequency component of intrauterine noise was produced by the transmission of the external ambient noise by maternal soft tissues. However, the ambient noise at those frequencies was consistently below the intrauterine background noise, suggesting that the intrauterine noise was probably not affected by the room background noise. Our data suggested that this low-frequency component of intrauterine noise was not due to maternal blood vessels, digestive system, or vocalization during which very different sound spectra were identified.

The effect of uterine activity on intrauterine background noise has not been systematically reported before. In this study we have not been able to demonstrate any significant effect of uterine activity on the fetal sound environment. Vince et al.,[4] using a radiohydrophone implanted on the neck of one fetal lamb, recorded sound pressure levels during the active phase of labor in one pregnant ewe. They described that uterine contractions were accompanied by a slow buildup of loud sound produced mainly by the maternal cardiovascular system, breathing sounds, and sound generated by the restless behavior of the ewes. These observations may have reflected the difficult and protracted labor of this particular ewe as one of her lambs was noted to be malpositioned. In this study, like others,[3, 4, 8, 9, 12] maternal vocalization and intermittent bowel sounds were the major acoustic stimuli available to the human fetus when the extrauterine sound environment was relatively quiet. From the work of Fifer and Moon,[13] it has been suggested that newborn infants tend to suck more often in response to maternal voice than in response to other female voices. Our data suggested that it is possible to speculate that this early

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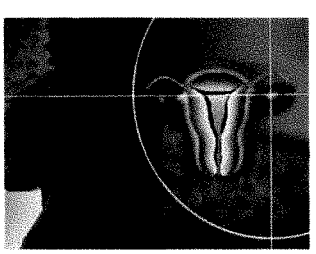


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responsiveness to mother's voice may be based on prenatal experience.

The data demonstrate that the intrauterine sound environment was relatively quiet (<60 dB at frequencies >100 Hz) interrupted by maternally generated sounds and not usually cardiovascular in origin. No significant difference was seen between uterine contraction and relaxation. Because of this relative quietness, it is possible that the fetal acoustic environment could be altered significantly during vibratory acoustic stimulation currently used in the evaluation of fetal health.[5] It remains to be determined to which sound intensity and frequencies the human fetus is exposed during such stimulation.

We thank Dr. John Patrick for his interest in this work, and Mrs. Maria De Sousa and Mr. John Ellis, PEng, for their excellent technical assistance.

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Effect of maternal-fetal movement on concentration of cells obtained at genetic amniocentesis

Stephen J. Carlan, MD, Peter Papenhausen, PhD, William F. O'Brien, MD, Marcello Pietrantoni, MD, Ronald A. Chez, MD, and Pamela Stephens, RN

Tampa, Florida

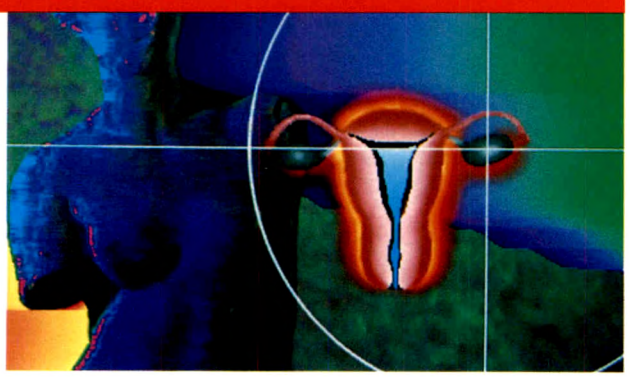
The number of viable amniotic fluid cells in the aliquot obtained at amniocentesis is an important determinant of the success of subsequent cell culture. However, cell concentration and viability are highly variable, even in samples of equivalent gestational age. We studied the effect of prescribed maternal position change or spontaneous fetal movement on the concentration, viability, and subsequent harvest time of amniotic fluid cells removed at genetic amniocentesis. Samples from 108 patients at 15 to 22 weeks' gestation were evaluated. We did not find a relationship between this type of maternal or fetal movement and the retrieval of amniotic fluid cells. (AM J OBSTET GYNECOL 1990;163:490-3.)

Key words: Amniocentesis, genetic karyotype, fetal motion

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6/1/21789

Amniocentesis is currently the most common method of obtaining a specimen of fetal cells for prenatal diagnosis.[1] Amniotic fluid cells (amniocytes) collected and successfully cultured provide information related to a wide range of fetal chromosomal, biochemical, and genetic disorders. A successful culture requires the pres-

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BRIEF SUMMARY

SYNAREL® Nasal Solution contains nafarelin acetate (2 mg/mL, expressed as nafarelin base), benzalkonium chloride glacial acetic acid, sodium hydroxide or hydrochloric acid, sorbitol, and purified water.

INDICATIONS AND USAGE: For management of endometriosis. Experience is limited to women 18 years and older treated for 6 months.

CONTRAINDICATIONS: Hypersensitivity to GnRH, GnRH agonist analogs or any excipients in SYNAREL; undiagnosed abnormal vaginal bleeding; pregnancy or possibility of pregnancy while taking the drug because SYNAREL may cause fetal harm when administered to a pregnant woman. If SYNAREL is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus; use in women who are breast feeding.

WARNINGS: Safe use in pregnancy has not been established clinically. Before starting treatment pregnancy must be excluded.

When used regularly at the recommended dose, SYNAREL usually inhibits ovulation and stops menstruation. Contraception is not insured, particularly if patients miss successive doses. Therefore, patients should use nonhormonal contraception. Advise patients to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, discontinue the drug; apprise patient of the potential risk to the fetus.

PRECAUTIONS Information for Patients: 1. Since menstruation should stop with SYNAREL, the patient should notify her physician if regular menstruation persists. Patients missing successive doses may experience breakthrough bleeding.

2. Patients should not use SYNAREL if pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of its ingredients.

3. Safe use in pregnancy has not been established. Therefore, a nonhormonal method of contraception should be used during treatment. If a patient becomes pregnant during treatment, she should discontinue the drug and consult her physician.

4. Adverse events occurring most frequently in clinical studies are associated with hypoestrogenism. Nasal irritation occurred in about 10% of patients.

5. Induced hypoestrogenic state results in a small loss in bone density over a 6-month treatment course. Some of this loss may not be reversible. During one six-month treatment period, this should not be important. In patients with major risk factors for decreased bone mineral content, i.e., chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, SYNAREL may pose additional risk. In these patients risks and benefits must be weighed carefully. Repeated courses of treatment with GnRH analogs are not advisable in patients with major risk factors for loss of bone mineral content.

6. Patients with intercurrent rhinitis should consult their physician for use of a topical nasal decongestant. If a topical nasal decongestant is required during treatment, it must be used at least 30 minutes after SYNAREL dosing to decrease the possibility of reducing drug absorption.

7. Retreatment cannot be recommended since safety data beyond 6 months are not available.

Drug Interactions: No pharmacokinetic-based drug-drug interaction studies have been conducted. Nafarelin acetate is a peptide primarily degraded by peptidase and not by cytochrome P-450 enzymes, and is only about 80% bound to plasma proteins at 4°C; therefore drug interactions would not be expected to occur.

Drug/Laboratory Test Interactions: SYNAREL in therapeutic doses suppresses the pituitary-gonadal system. Normal function is usually restored 4–8 weeks after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions during treatment and up to 4–8 weeks after discontinuation of SYNAREL may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in rats and mice at intramuscular doses up to 110 times and 560 times the maximum recommended human intranasal dose respectively. These multiples of the human dose are based on the relative bioavailability of the drug by the two routes of administration. As with other GnRH agonists, nafarelin acetate given to laboratory rodents at high doses for prolonged periods induced hyperplasia and/or neoplasia of endocrine organs. At 24 months, there was an increase in the incidence of pituitary tumors (adenoma/carcinoma) in high-dose female rats and a dose-related increase in male rats. There was an increase in pancreatic islet cell adenomas in both sexes, and in benign testicular and ovarian tumors in the treated groups. There was a dose-related increase in benign adrenal medullary tumors in treated female rats. In mice, there was a dose-related increase in Harderian gland tumors in males and an increase in pituitary adenomas in high-dose females. No metastases of these tumors were observed. It is known that tumorigenicity in rodents is particularly sensitive to hormonal stimulation.

Mutagenicity studies using bacterial, yeast, and mammalian systems provided no evidence of mutagenic potential.

Reproduction studies in male and female rats have shown full reversibility of fertility suppression when treatment was discontinued after continuous administration for up to 6 months.

Pregnancy, Teratogenic Effects: *Pregnancy Category X.* Intramuscular SYNAREL was administered to rats throughout gestation at about 0.5, 2, and 7 times the maximum recommended human intranasal dose based on the relative bioavailability by the two routes of administration. An increase in major fetal abnormalities was seen in 4/80 fetuses at the highest dose. A similar study at the same doses in rats and studies in mice and rabbits at doses up to 600 μg/kg/day and 0.18 μg/kg/day, respectively, failed to demonstrate an increase in fetal abnormalities after administration throughout gestation. In rats and rabbits, there was a dose-related increase in fetal mortality and a decrease in fetal weight with the highest dose.

Nursing Mothers: It is not known whether SYNAREL is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of SYNAREL on lactation and/or the breastfed child have not been determined, SYNAREL should not be used by nursing mothers.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most frequently reported adverse reactions were those related to hypoestrogenism. In controlled studies comparing SYNAREL (400 μg/day) and danazol (600 or 800 mg/day), the following adverse reactions were most frequently reported and thought to be drug-related.

Hypoestrogenic: hot flashes (SYNAREL 90%, danazol 69%), decreased libido (22%, 7%), vaginal dryness (19%, 7%), headaches (19%, 21%), emotional lability (15%, 18%), insomnia (8%, 4%); **Androgenic:** acne (13%, 20%), myalgia (10%, 23%), reduced breast size (10%, 16%), edema (8%, 23%), seborrhea (8%, 17%), weight gain (8%, 28%), hirsutism (2%, 6%), increased libido (1%, 6%); **Local:** nasal irritation (10%, 3%); **Miscellaneous:** depression (2%, 5%), weight loss (1%, 3%).

Less than 1% of patients experienced paresthesia, palpitations, chloasma, maculopapular rash, eye pain, urticaria, asthenia, lactation, breast engorgement, and arthralgia. In clinical trials, immediate hypersensitivity thought to be possibly or probably related to nafarelin occurred in 3 (0.2%) of 1509 healthy subjects or patients.

Changes in Bone Density: After 6 months' treatment vertebral trabecular bone density and total vertebral bone mass, measured by quantitative computed tomography (QCT), decreased by an average of 8.7% and 4.3%, respectively, compared to pretreatment levels. There was partial recovery of bone density post-treatment; the average trabecular bone density and total bone mass were 4.9% and 3.3% less than pretreatment levels, respectively. Total vertebral bone mass, measured by dual photon absorptiometry (DPA), decreased by a mean of 5.9% at end of treatment. Mean total vertebral mass, re-examined by DPA 6 months post-treatment, was 1.4% below pretreatment levels. There was little, if any, decrease in the mineral content in compact bone of the distal radius and second metacarpal. Use for longer than the recommended 6 months or in presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Changes in Laboratory Values: *Plasma enzymes.* During clinical trials SGOT and SGPT levels were more than twice the upper limit of normal in only one patient each. There was no other evidence of abnormal liver function and levels returned to normal after treatment was stopped.

Lipids. At enrollment and at end of treatment, 9% of patients on SYNAREL 400 μg/day and 2% on danazol had total cholesterol values above 250 mg/dL.

Of those with pretreatment cholesterol values below 250 mg/dL, 6% on SYNAREL and 18% on danazol had post-treatment values above 250 mg/dL.

Mean (±SEM) pretreatment values for total cholesterol from all patients were 191.8 (4.3) mg/dL in the SYNAREL group and 193.1 (4.6) mg/dL in the danazol group. At the end of treatment, mean values from all patients were 204.5 (4.8) mg/dL in the SYNAREL group and 207.7 (5.1) mg/dL in the danazol group. These increases from pretreatment values were significant ($p < 0.05$) in both groups.

Triglycerides were increased above the upper limit of 150 mg/dL in 12% of the patients on SYNAREL and in 7% of the patients on danazol.

At the end of treatment, no patients on SYNAREL had abnormally low HDL cholesterol fractions (< 30 mg/dL) compared with 43% of patients on danazol. No patients on SYNAREL had abnormally high LDL cholesterol fractions (> 190 mg/dL) compared with 15% of those on danazol. There was no increase in the LDL/HDL ratio in patients on SYNAREL, but approximately a 2-fold increase in the LDL/HDL ratio in patients on danazol.

Other changes. In comparative studies, the following changes were seen in approximately 10% to 15% of patients. SYNAREL was associated with elevations of plasma phosphorous and eosinophil counts, and decreases in serum calcium and WBC counts. Danazol therapy was associated with an increase of hematocrit and WBC.

OVERDOSAGE: At present there is no clinical evidence of adverse effects following overdosage of GnRH analogs.

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ence of adequate numbers of viable amniocytes. However, the concentration of cells and the proportion that are viable may vary widely between samples.[2]

A mechanism to increase the concentration of viable cells could increase the incidence of success and decrease the time to harvest. Controlling for gestational age, we studied the effect of a prescribed maternal position change or spontaneous fetal movement on the concentration, viability, and harvest time of cells obtained from second-trimester amniocenteses.

Material and methods

A total of 108 patients with singleton gestations scheduled for genetic amniocentesis between 15 and 22 weeks' gestation were enrolled in the study. Gestational age, placental location, fetal viability, and fetal number were confirmed with ultrasonography. The indications for the procedure included: advanced maternal age, 85 patients (78%); previous offspring with genetic disorders, 10 (9%); low maternal serum α-fetoprotein, 6 (5%), and others, 7 (6%). After informed consent was obtained the patient was randomized to either turn over 360 degrees on the examination table within 60 seconds before amniocentesis, or not turn. An amniocentesis using sterile technique with a 21-gauge spinal needle under continuous ultrasonographic guidance was then performed by either a fellow or faculty member of the Division of Obstetrics. A 5 MHz linear transducer (GE 3000) was used for all procedures. The placenta was avoided if possible. No aspirated fluid was discarded. Any specimen containing any degree of visible blood (even if it cleared immediately) was considered a bloody tap. Any fetal movement (regardless of the character of movement) that occurred during the procedure was noted. Normal fetal heart motion was ensured after the procedure before patient discharge. The amniotic fluid samples were immediately placed in plastic sterile containers at room temperature. Within 4 hours (before centrifugation) the fluid sample was studied for viability, cell type, and concentration. Viability was determined with trypan blue exclusion, and cell concentrations were calculated with a hemacytometer under light microscopy. Cell type was recorded as either epithelioid (large and flat), or mesenchymal (small and round).[3] Harvest times were adjusted for weekend work schedules. Results were analyzed with analysis of variance, with differences among the groups tested by use of Duncan's multiple range test.

Results

The average maternal age was 36 years (range, 18 to 41 years), and the average weight was 154 pounds (range, 105 to 342 pounds). Racial distribution of the patients was as follows: 95 white, seven black, five Hispanic, and one Oriental. Two punctures were required in five patients (4.6%), and there was a bloody tap in nine patients (8.3%). An average of 20 ml (range, 12 to 30 ml) of amniotic fluid was obtained. All cell cultures were successful, and there were no karyotypic abnormalities or major congenital anomalies detected by ultrasonography in this group of patients.

Table I. Distribution of gestational age and percentage of live cells

Completed gestational wk	*N*	*%*	*Average % live cells*	*Mean harvest time (days)*
15	17	16%	73	7.5
16	44	41%	66	7.7
17	18	17%	76	7.8
18	13	12%	72	7.0
19	8	7%	61	7.3
20	8	7%	53	6.8

Table II. Maternal-fetal movement groups

Group	*Maternal turn*	*Fetal movement*
1	Yes	Yes
2	Yes	No
3	No	Yes
4	No	No

When patients were grouped by gestational age, there was a trend toward decreasing concentration of live cells, especially in samples obtained after 18 completed weeks. Because of the relatively small sample size at this gestational age, however, we could not demonstrate a statistically significant gestational age effect on the number of live cells recovered or harvest time (Table I).

The patients were divided into four groups based on occurrence of maternal or fetal movement, or both (Table II). Mean cell type concentration and mean harvest time among the four groups are compared in Table III. Similar information was recorded after elimination of the 11 patients who had either a bloody tap or more than one needle insertion (Table IV). There was no statistical difference noted among the four groups. Similarly, when the groups were evaluated by gestational age, there was no statistically significant difference in the observed parameters.

Comment

There are several reasons for attempting to increase the number of viable cells obtained at amniocentesis. First, daughter cells in vitro may undergo secondary culture-induced chromosomal changes. Therefore it is important to have a clonal (in situ) evaluation of a large base of primary amniocytes to differentiate between true mosaicism and pseudomosaicism.[4-6] Second, increased cell numbers allow more flasks or cover slips

Diabetic ketoacidosis and insulin resistance with subcutaneous terbutaline infusion: A case report

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Diabetic ketoacidosis may occur in women treated with intravenous β-sympathomimetic agents for tocolysis. We describe diabetic ketoacidosis and transient severe insulin resistance in a woman with diabetes who was treated with subcutaneous terbutaline infusion. Subcutaneous terbutaline infusion may precipitate transient insulin resistance and diabetic ketoacidosis in women with diabetes. (AM J OBSTET GYNECOL 1990;163:509-10.)

Key words: Diabetes, ketoacidosis, terbutaline, tocolysis, insulin resistance

Diabetic ketoacidosis is a well-known complication of intravenous tocolysis with the β-sympathomimetic agents ritodrine and terbutaline.[1] Diabetic ketoacidosis has not been described with chronic oral use of either drug. Continuous subcutaneous infusion of terbutaline sulfate has recently been introduced for the treatment of preterm labor.[2] We report a patient with insulin-dependent diabetes in whom diabetic ketoacidosis developed during treatment with subcutaneous terbutaline infusion.

Case report

A 25-year-old woman with a 15-year history of insulin-dependent diabetes mellitus was admitted with uterine contractions noted on home uterine monitoring at 25 weeks of a twin gestation. Before admission her diabetes was well controlled with 50 to 60 units of insulin per day. Initial treatment with magnesium sulfate infusion was unsuccessful and treatment was begun with subcutaneous terbutaline via a battery-powered infusion pump (MiniMed model 404, MiniMed Technologies, Sylmar, Calif.) at a rate of 0.94 mg/24 hours with additional 0.25 mg boluses as needed. Total terbutaline requirements were between 2.0 and 3.0 mg/24 hours. Magnesium sulfate infusion was tapered and discontinued.

Before beginning the terbutaline infusion, the patient's plasma glucose level remained between 80 and 120 mg/dl on a constant infusion of 1 U/hr of regular insulin with 100 ml/hr of 5% dextrose. With addition of terbutaline her insulin infusion was increased to 4 U/hr. Despite this increase her plasma glucose level rose to 355 mg/dl with marked ketonuria and acidosis (bicarbonate, 11 mEq/L). Over the next 24 hours she required 110 units of insulin to resolve the ketoacidosis. At this time she began a diabetic diet and preprandial doses of regular insulin and HS NPH. On the third day of terbutaline infusion she required 126 units of insulin in divided doses. Insulin requirements than began to decrease; by the seventh day of terbutaline infusion her total daily insulin requirement was 77 units. Terbutaline infusion was maintained until the thirty-fifth week of pregnancy when cesarean section was performed. There were no further incidents of hyperglycemia or ketoacidosis.

Comment

Intravenous magnesium sulfate tocolysis is often successful in women with diabetes but hospitalization and careful monitoring are necessary. Intravenous but not oral administration of β-sympathomimetic agents is well known to cause metabolic decompensation with ketoacidosis in women with diabetes.

Oral tocolysis does not provide adequate maintenance for 40% to 50% of women with preterm labor and often repeat hospitalization for parenteral therapy is necessary. The development of portable, battery-powered, infusion pumps has made chronic parenteral therapy with subcutaneous terbutaline a viable alternative when oral tocolysis is unsuccessful.

Insulin resistance and ketoacidosis developed rapidly in our patient during treatment with terbutaline in a total dose of 2 to 3 mg per 24 hours, dramatically less than the usual intravenous or oral terbutaline dose of 40 to 60 mg/24 hours. Insulin requirements remained elevated for several days but fell to near-basal levels despite continued terbutaline infusion. This finding is probably explained by downregulation of adrenergic receptors with a decrease in hepatic glucose output, lipolysis, and ketogenesis.

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Table III. Results of the effect of movement on amniotic fluid cell concentration and harvest time

Group	Mean gestational age (wk)	Mean (% of total)						
		N	%	Epithelioid*	Mesenchymal*	Dead cells*	Total cells*	Harvest time (days)
1	16.6	39	36%	6,846 (29%)	9,987 (42%)	6,782 (29%)	23,608	7.85
2	16.6	19	17%	6,315 (25%)	9,315 (37%)	9,315 (37%)	24,947	7.7
3	17.0	35	32%	9,050 (31%)	10,842 (37%)	8,850 (31%)	28,742	7.26
4	17.0	15	14%	6,483 (25%)	11,800 (46%)	7,316 (28%)	25,599	7.40

*Cells per cubic milliliter.

Table IV. Results of the effect of movement on amniocyte concentrations in blood-stained, single-needle puncture samples

Group	Mean gestational age (wk)	N	%	Mean concentration epithelioid*	Mean concentration mesenchymal*	Mean concentration dead cells*	Mean concentration total cells*	Mean harvest time (days)
1	16.6	36	37%	7,208	10,125	6,444	23,777	7.7
2	16.7	17	17.5%	6,470	9,970	9,823	26,264	7.6
3	17.2	31	32%	9,096	11,112	9,185	29,395	7.1
4	16.8	13	13.5	6,711	11,326	7,090	25,134	7.2

*Cells per cubic milliliter.

to be set up, thus increasing the number of diagnostic mitoses and decreasing the time for completion. Finally, if a method of increasing the concentration of viable amniotic fluid cells could be discovered, less fluid would be required, which would be especially helpful in early amniocentesis.[7]

Resolution with current real-time ultrasonography is frequently adequate to discern turbulence echoes that appear when a second-trimester fetus moves suddenly. Agitation of a stable or resting system characterized by cells suspended in a liquid would intuitively appear to increase the likelihood of recovering more cells. The turbulence created should resuspend cells that have settled out, thus increasing the chance of their being obtained with the fluid sample. Therefore sampling the fluid immediately after a maternal movement, or during a fetal movement, should improve the cell yield.

In this study fetuses were observed to move during the procedure 68% of the time, and a maternal movement was prescribed 52% of the time. However, neither of these movements, alone or in combination, affected the concentration of cells in the sample obtained. Moreover, the specific type of cell recovered does not appear to be related to movement.

There are several other factors that may have influenced our results. Although there are different degrees of fetal movement, we did not specify the character of movement necessary to qualify for the "fetal movement" group. Any observed fetal movement was considered adequate. It is possible that a sudden forceful movement may create more agitation than the slow passive roll. Because turbulence echoes were not specifically documented, the data may not accurately reflect the effect of fluid agitation on cell recovery. Unfortunately, clear documentation of turbulence echoes, even if present, is not possible with every patient. The resolution of the ultrasonographic signal suffers as the distance from transducer to target lengthens. Thus turbulence may go unnoticed in obesity, advancing gestation, or in the deep pockets of the amniotic sac.

Second, a simple 360-degree maternal turn on the table immediately before amniocentesis may be inadequate to eliminate a "settling-out" effect, if present. However, more vigorous activity may be unacceptable to the patient.

Finally, the location of the needle point was generally just below the chorionic plate. This may not have been deep enough to detect any change in the amniocyte concentration produced by movement.

We conclude that agitation of amnionic fluid as produced by maternal or fetal movement in our protocol did not affect mean cell concentration, type, or harvest time obtained at genetic amniocentesis between 15 and 22 weeks. However, optimization of cell yield through a more effective combination of agitation and aspiration site selection may still be possible.

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Continuous subcutaneous terbutaline infusion is an exciting new development in treatment of preterm labor. Its use is associated with a significant, albeit transitory, increase in glucose intolerance. This effect may be of little significance for the pregnant woman with normal glucose tolerance. For the woman with impaired glucose tolerance, gestational diabetes, or preexisting insulin-dependent diabetes, subcutaneous terbutaline may cause severe metabolic decompensation with hyperglycemia and ketoacidosis. Careful monitoring of plasma glucose and urine ketones is necessary with the institution of continuous subcutaneous terbutaline tocolysis.

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A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis

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A randomized, clinical trial was conducted to evaluate the spermicidal agent nonoxynol 9 as prophylaxis for sexually transmitted diseases. Eight hundred eighteen women using birth control who attended a sexually transmitted disease clinic were evaluated monthly for trichomoniasis, candidiasis, and bacterial vaginosis for 6 months. Women using the active spermicide experienced a somewhat lower incidence rate of trichomoniasis (relative rate 0.83; 95% confidence interval 0.61 to 1.12) and bacterial vaginosis (relative rate 0.86; 95% confidence interval 0.69 to 1.12) as compared with placebo users. The rate of candidiasis was nearly identical for spermicide and placebo users (relative rate 1.02; 95% confidence interval 0.77 to 1.35). The number of sexual partners during the preceding month was related directly to the occurrence of trichomoniasis ($p = 0.047$) and bacterial vaginosis ($p = 0.009$) but not candidiasis ($p = 0.99$). Subjects using oral contraceptives experienced a statistically significant lower rate of trichomoniasis than did women using an intrauterine contraceptive device or who had had a tubal ligation (relative rate 0.56; 95% confidence interval 0.39 to 0.81). (Am J Obstet Gynecol 1990;163:510-4.)

Key words: Trichomoniasis, candidiasis, bacterial vaginosis, spermicide, oral contraceptives

Trichomoniasis, bacterial vaginosis, and candidiasis are common genital infections. Sexual transmission is the major cause of trichomoniasis[1] and probably is involved in most cases of bacterial vaginosis[2] and candidiasis.[3] However, the data regarding the evaluation of strategies for personal protection against these infections are limited. For example, although spermicides have been shown to inhibit the growth of *Trichomonas vaginalis* in vitro,[4] we are not aware of any clinical trials of spermicidal agents as a prophylaxis against trichomoniasis, bacterial vaginosis, or candidiasis. Furthermore, epidemiologic studies have found that spermicidal gels lower the risk of gonorrhea[5] and chlamydia.[6]

The prophylactic potential of a vaginal gel containing nonoxynol 9 on trichomoniasis, bacterial vaginosis, and candidiasis was evaluated in a randomized placebo-controlled trial. The design of the study also allowed

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evaluation of the role of sexual transmission and oral contraceptive use on these infections.

Methods

The study design is described in detail elsewhere.[6, 7] Briefly, the study subjects were recruited from the sexually transmitted disease (STD) clinic of the Jefferson County Department of Health, Birmingham, from April 1984 through January 1986. The women volunteered to participate in a randomized, clinical trial of the spermicidal agent nonoxynol 9 as a prophylaxis against gonococcal and chlamydial infections. The subjects ranged in age from 19 to 29 years, were not pregnant, and were using and planned to continue using contraception (oral contraceptives, intrauterine contractive device, or a previous tubal ligation) for the next 6 months. This study was approved by the University's Institutional Review Board.

Subjects were assigned randomly to a group that was asked to use a commercially available spermicide containing a 3% concentration of nonoxynol 9 (408 women) or to a group using the vehicle for this product (410 women). Subjects were scheduled for monthly follow-up visits during a 6-month observation period. They were provided a calendar diary and instructed to keep a record of each sexual encounter they had during the previous month and whether the vaginal gel had been used. At each visit subjects were examined by a clinical nurse practitioner who palpated for enlarged lymph nodes, looked for skin lesions, inspected the perineal area, and performed a vaginal speculum examination and a bimanual pelvic examination. Endocervical cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were performed at each follow-up visit. If a subject had either of these two infections or any other STD, the appropriate treatment was provided. Subjects who were taking antibiotics or using intravaginal antibacterial or antifungal preparations were temporarily suspended from the trial until the prescribed antimicrobial therapy had ended.

The diagnosis of trichomoniasis was made by wet preparation if motile *T. vaginalis* organisms were present with or without an abnormal vaginal discharge.

Candidiasis was diagnosed by potassium hydroxide preparation showing yeast and/or hyphae with or without classic vaginal discharge or appearance.

Bacterial vaginosis was diagnosed by means of a positive amine test, a wet preparation showing clue cells, and an abnormal grayish discharge. Bacterial vaginosis was diagnosed only if at least two of the three criteria were met. pH was not evaluated because the study was conducted before the recommendation for inclusion of pH as a diagnostic criterion for bacterial vaginosis.

Statistical methods. The Cox proportional hazards model was used to estimate the relative rate of each infection as a function of exposure.[8] For a dichotomous exposure such as oral contraceptive or spermicide use, the relative rate is interpreted as the incidence rate of infection among the exposed divided by that among the unexposed. An advantage of the Cox model is that it allows for simultaneous control of many potential confounding (distorting) factors.

Most models included terms for age, race, spermicide category, birth control method, and sexual activity. However, since the study is randomized with respect to spermicide assignment, it is not necessary to adjust for these factors in the analysis pertaining to spermicide use (Table I). For this analysis the relative rate is estimated simply by dividing the infection rate among active spermicide users by the rate among placebo users. A confidence interval for the relative rate was obtained through the use of a method described by Rothman.[9]

If a subject was found to have trichomoniasis, candidiasis, or bacterial vaginosis at the initial examination, she was excluded from all subsequent analyses of that specific infection. Furthermore, if a woman was diagnosed with one of the three infections during the follow-up period, that event was counted in the analysis, but she was excluded from further analyses pertaining to that specific infection. Only first infections diagnosed during the observation period were counted because, although treatment was always provided after the diagnosis of these infections, test of cure was not always ascertained. Thus, to avoid counting the same infection twice, repeated infections were not considered. This procedure explains the slightly different length of the observation periods for the three infections.

Spermicide assignment and birth control method remained fixed during the 6-month observation period. On the other hand, the number of partners and the number of episodes of sexual intercourse each month varied during the follow-up period and were modeled accordingly. All p values in the report are two-tailed and 95% confidence intervals are used.

Results

Of the 818 subjects participating in the study, 617 were using oral contraceptives, 158 had been sterilized, and 43 were using intrauterine contraceptive devices. The median age of subjects was 23 years; 89% were black and the remainder were white; 18% were married.

Spermicide use. The effect of the use of the active spermicide compared with the placebo on the occurrence of trichomoniasis, bacterial vaginosis, and candidiasis is shown in Table I. Subjects using the active spermicide experienced a lower incidence rate of trichomoniasis and bacterial vaginosis, but the decrease is not statistically significant, either for trichomoniasis ($p = 0.21$) or for bacterial vaginosis ($p = 0.18$). The

Assessment of cerebral hemodynamics in pregnant women by internal carotid artery pulsed Doppler velocimetry

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To date, no studies have been done of serial changes in maternal cerebral hemodynamics during pregnancy. We used the noninvasive method of Doppler velocimetry to assess cerebral hemodynamics in pregnant women. Velocimetry measurements of the internal carotid artery were performed in 17 normal nonpregnant women and 77 women with uncomplicated pregnancies with a 4 MHz pulsed Doppler ultrasound system. Peak systolic and mean velocities in the first and second trimesters were almost the same as those in nonpregnant women, whereas they became slower in the third trimester. Pulsatility index from 4 to 31 weeks' gestation was significantly higher than in nonpregnant women, but fell to the nonpregnant value after 32 weeks. Doppler velocimetry was found to be an extremely useful method of cerebrohemodynamic evaluation in pregnant women. (AM J OBSTET GYNECOL 1990;163:494-8.)

Key words: Doppler, internal carotid artery, cerebral circulation, pregnancy

Marked changes in the cardiovascular system occur during pregnancy. Cardiac output and blood flow of organs such as uterus and kidney change drastically in pregnant women and have been measured by different methods. Little is known about cerebral hemodynamics in pregnancy,[1] although it is believed that pregnancy increases the risk of cerebrovascular compromise.[2] Traditional techniques for measurement of cerebral circulation are invasive to both mother and fetus and are time-consuming and expensive. Satomura and Kaneko[3] first used Doppler ultrasound for investigation of blood flow in 1960. Since then Doppler velocimetry has been used to measure the hemodynamics of various organs. In internal medicine and neurosurgery, Doppler velocimetry is used to evaluate cerebrovascular complications, especially stenosis and occlusions of main cerebral arteries. We present a preliminary study of cerebral hemodynamics in pregnancy using Doppler velocimetry of the internal carotid artery.

Material and methods

This study consisted of 17 nonpregnant women and 77 pregnant women referred from our outpatient clinic. Informed oral consent was obtained from all subjects. Pregnant women with a single fetus in utero were studied between 5 and 40 weeks' gestation. All had accurate pregnancy dating by early ultrasound biometry and had uncomplicated pregnancies.

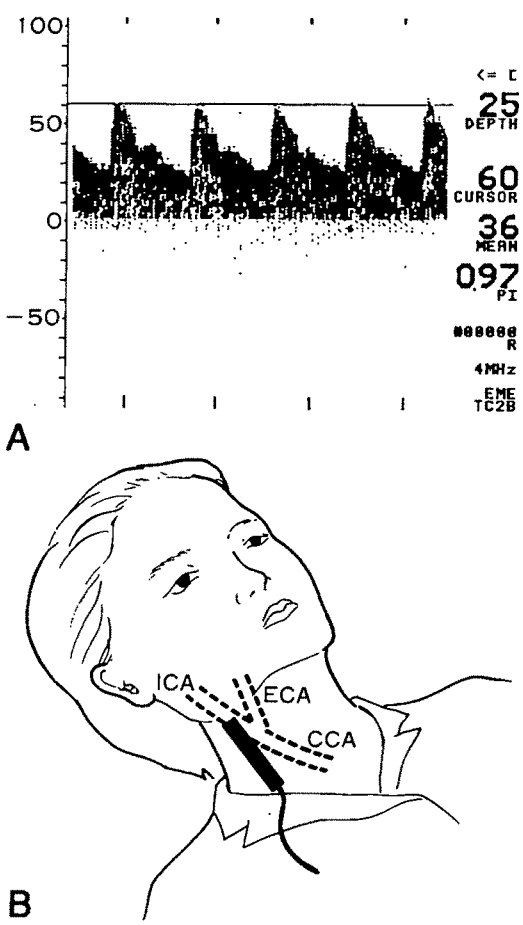


Fig. 1. A, Velocity wave forms of internal carotid artery. Values on the right indicate (from top to bottom) gate depth, peak systolic velocity, mean velocity and pulsatility index. **B,** Schematic view of internal carotid velocimetry. Probe is positioned at the height of the angle of the submandibular bone in order for the beam to parallel the artery. *ICA,* internal carotid artery; *ECA,* external carotid artery; *CCA,* common carotid artery.

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Table I. Number, rates, and relative rates of trichomoniasis, bacterial vaginosis and candidiasis, according to spermicide assignment

	Placebo			*Spermicide*				
Infection	*No. of events*	*Woman months*	*Incidence rate**	*No. of events*	*Woman months*	*Incidence rate**	*Relative rate*	*95% Confidence interval*
Trichomoniasis	92	1534	6.0	79	1593	5.0	0.83	0.61-1.12
Bacterial vaginosis	170	1249	13.6	147	1254	11.7	0.86	0.69-1.07
Candidiasis	98	1526	6.4	100	1527	6.5	1.02	0.77-1.35

*Number of infections per 100 women per month.

Table II. Number, rates, and relative rates of trichomoniasis, bacterial vaginosis, and candidiasis, by number of partners

Infecton	*No. of partners*	*No. of events*	*Woman months*	*Incidence rate**	*Relative rate†*	*95% Confidence interval†*
Trichomoniasis	0-1	133	2442	5.4	1.0	
	2	19	324	5.9	1.12	0.69-1.82
	≥3	13	157	8.3	1.91	1.06-3.45
Bacterial vaginosis	0-1	239	1963	12.2	1.0	
	2	38	266	14.3	1.14	0.81-1.62
	≥3	27	122	22.1	1.77	1.17-2.69
Candidiasis	0-1	159	2377	6.7	1.0	
	2	21	308	6.8	1.03	0.66-1.52
	≥3	10	170	5.9	0.88	0.46-1.68

*Number of infections per 100 women per month.

†From a proportional hazard model including terms for age, race, spermicide use, birth control method, and number of episodes of sexual intercourse.

infection rate of candidiasis was nearly identical for spermicide and placebo users. The results in Table I were nearly identical to those obtained from the use of a proportional hazards model, which allowed for the control of potentially confounding variables.

The percentage of times that the gel was used during vaginal intercourse was used as a measure of compliance. However, the relative rate of each infection for spermicide users compared with placebo users did not decrease consistently with increasing compliance.

Sexual activity. The number of partners and the number of episodes of sexual intercourse per month were used as measures of sexual activity. The number of sexual partners during the month preceding a follow-up visit (Table II) was related directly to the occurrence of trichomoniasis and bacterial vaginosis. A test for trend was statistically significant both for trichomoniasis ($p = 0.047$) and for bacterial vaginosis ($p = 0.009$). On the other hand, no positive association was found between number of sexual partners and the incidence of yeast infections (trend test: $p = 0.99$).

In contrast to the number of sexual partners, there was an inverse relation between the monthly number of episodes of sexual intercourse and trichomoniasis (trend test: $p = 0.004$) and candidiasis (test for trend: $p = 0.07$). There was little or no association between the rate of bacterial vaginosis and number of sexual episodes (trend test: $p = 0.88$) (Table III).

The use of antibiotics during the month preceding a follow-up visit was unrelated to the occurrence of candidiasis or to the other STDs. Therefore antibiotic use did not confound any of the associations described.

Oral contraceptive use. Women using oral contraceptives experienced a 44% lower infection rate of trichomoniasis (Table IV) than did women using an IUD or who had had a tubal ligation ($p = 0.002$). The relative rate of bacterial vaginosis for oral contraceptive users compared with nonusers also was below unity, but this deficit was not statistically significant ($p = 0.20$). On the other hand, the rate of candidiasis was higher among oral contraceptive users than nonusers, but this increase also was not statistically significant ($p = 0.21$).

Comment

Our results suggest that the use of a spermicide containing nonoxynol 9 protects against trichomoniasis and bacterial vaginosis. However, the magnitude of the protection was small and, since the findings are not statistically significant, they might be due to chance. In a recent cross-sectional study of women attending a

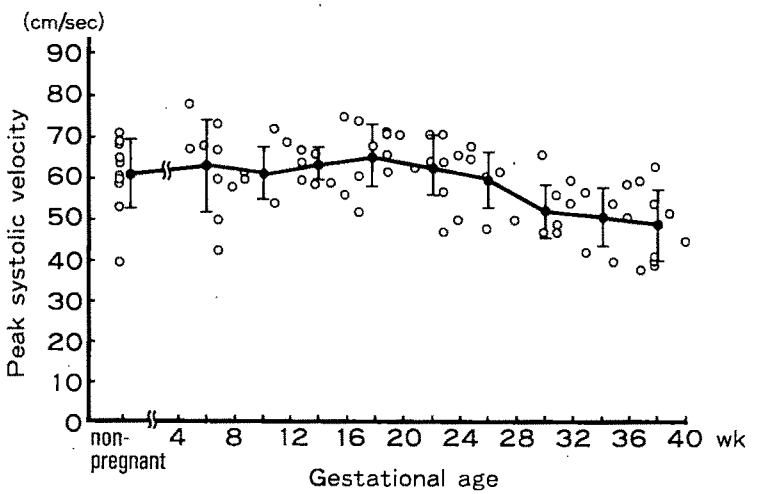


Fig. 2. Peak systolic velocity in internal carotid artery in nonpregnant women and women with uncomplicated pregnancies. *Open circles* indicate mean values of right and left carotid arteries. *Bars* represent mean ± SD.

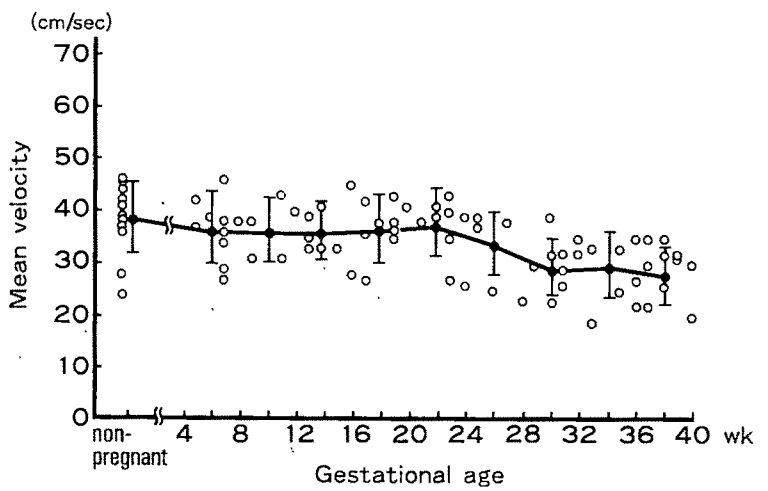


Fig. 3. Mean velocity in internal carotid artery in nonpregnant women and women with uncomplicated pregnancies. *Open circles* indicate mean values of right and left carotid arteries. *Bars* represent mean ± SD.

Table I. Parity and mean age of nonpregnant and pregnant women

	Weeks' gestation	*Women (n)*	*Primiparous (n)*	*Multiparous (n)*	*Age (yr) (mean ± SD)*
Nonpregnant		17	10	7	28.3 ± 3.9
Pregnant	4-7	9	5	4	27.8 ± 3.2
	8-11	5	2	3	26.6 ± 3.0
	12-15	7	4	3	28.3 ± 2.7
	16-19	10	5	5	26.3 ± 4.0
	20-23	8	3	5	27.9 ± 1.9
	24-27	7	3	4	28.6 ± 2.4
	28-31	8	5	3	29.1 ± 2.3
	32-35	7	4	3	28.3 ± 2.7
	36-40	16	8	8	28.1 ± 2.7
	Total	77	39	38	27.9 ± 2.9

Table III. Number, rates, and relative rates of trichomoniasis, bacterial vaginosis, and candidiasis, by number of episodes of sexual intercourse

Infection	*No. of sexual episodes*	*No. of events*	*Woman months*	*Incidence rate**	*Relative rate†*	*95% Confidence interval†*
Trichomoniasis	0-3	72	1008	7.1	1.0	
	4-5	32	543	5.9	0.81	0.53-1.25
	6-8	31	608	5.1	0.68	0.44-1.05
	≥9	30	764	3.9	0.46	0.29-0.71
Bacterial vaginosis	0-3	98	824	11.9	1.0	
	4-5	58	456	12.7	1.06	0.76-1.48
	6-8	76	485	15.7	1.28	0.95-1.75
	≥9	72	586	12.3	0.90	0.66-1.23
Candidiasis	0-3	70	961	7.3	1.0	
	4-5	43	555	7.7	1.25	0.84-1.84
	6-8	45	613	7.3	1.16	0.79-1.69
	≥9	32	726	4.4	0.63	0.41-0.97

*Number of infections for 100 women per month.

†From a proportional hazard model also including age, race, spermicide use, birth control method, and number of partners.

Table IV. Number, rates, and relative rates of trichomoniasis, bacterial vaginosis, and candidiasis, by birth control method

Infection	*Birth control method*	*No. of events*	*Woman months*	*Incidence rate**	*Relative rate†*	*95% Confidence interval†*
Trichomoniasis	IUD plus tubal ligation	60	686	8.7	1.0	
	Oral contraceptive	111	2442	4.5	0.56	0.39-0.81
Bacterial vaginosis	IUD plus tubal ligation	87	576	15.1	1.0	
	Oral contraceptive	230	1927	11.9	0.84	0.63-1.10
Candidiasis	IUD plus tubal ligation	41	813	5.0	1.0	
	Oral contraceptive	157	2240	7.0	1.28	0.87-1.90

IUD, Intrauterine contraceptive device.

*Number of infections for 100 women per month.

†From a proportional hazard model also including terms for age, race, spermicide use, and sexual activity.

reproductive clinic, Feldblum et al.[10] reported that the prevalence of trichomoniasis and bacterial vaginosis was significantly lower among spermicide users than oral contraceptive users. However, since about 80% of the spermicide users in their study also used diaphragms, the protective effects may be due to diaphragms, or to a combination of the diaphragm and spermicides, rather than to spermicides alone. Another limitation of that study is that the associations were not adjusted for sexual activity, so that their findings may reflect simply increased sexual activity among oral contraceptive users compared with spermicide users. Our study subjects did not use diaphragms and our findings are not confounded by level of sexual activity. We also found a protective effect of spermicide use against trichomoniasis and bacterial vaginosis, but the protection was appreciably less than that reported by Feldblum et al., suggesting that their findings may have been confounded by diaphragm use and sexual activity. Nonetheless, the two studies taken together provide support for the idea that spermicide use protects against trichomoniasis and bacterial vaginosis.

Neither we nor Feldblum et al. found an association between spermicide use and candidiasis, whereas Rosenberg et al.[11] found that women using a contraceptive sponge containing nonoxynol 9 were more likely to be infected with *Candida* than women not using the sponge. These findings suggest that nonoxynol 9 alone does not increase the rate of infection by *Candida.* However, a combination of nonoxynol 9 and the sponge may increase the rate of candidiasis, or the apparent discrepancy between our findings and those of Rosenberg et al. may be due to different characteristics of the study subjects in Bangkok and in Birmingham.

Trichomoniasis has long been considered a STD.[12] Recent studies have demonstrated the absence of trichomoniasis in virginal female adolescents compared with sexually active adolescent girls.[13, 14] On the contrary, candidiasis and bacterial vaginosis have been isolated both in virgin women and in sexually active women.[14] Nonetheless, it is generally held that a high level of sexual activity also is a risk factor for candidiasis and bacterial vaginosis.

Our study confirms that number of sexual partners is a risk factor for trichomoniasis and bacterial vaginosis (Table II). However, number of partners was not as-

Table II. Internal carotid arterial mean velocity, peak systolic velocity and pulsatility index in nonpregnant women and women with uncomplicated pregnancies

Average of right and left arteries	*Nonpregnant (n = 17)*	*Pregnant women*					
		4-7 wk (n = 9)	*8-11 wk (n = 5)*	*12-15 wk (n = 7)*	*16-19 wk (n = 10)*	*20-23 wk (n = 8)*	*24-27 wk (n = 7)*
Mean velocity (cm/sec)	38.1 ± 6.3	36.4 ± 5.6	36.2 ± 4.6	36.3 ± 3.3	36.9 ± 5.6	38.0 ± 4.7	34.0 ± 5.6
Mean side difference (cm/sec)	5.5	5.3	5.2	6.9	6.6	6.0	3.4
Peak systolic velocity (cm/sec)	61.2 ± 8.1	63.2 ± 11.0	61.2 ± 6.0	63.4 ± 3.8	65.7 ± 7.3	63.5 ± 7.8	60.0 ± 7.3
Mean side difference (cm/sec)	6.3	7.1	8.0	11.1	8.9	8.0	4.0
Pulsatility index	0.80 ± 0.08	0.92* ± 0.09	0.96† ± 0.05	0.99† ± 0.07	1.02† ± 0.12	0.98† ± 0.12	1.01† ± 0.10
Mean side difference	0.09	0.07	0.09	0.06	0.05	0.04	0.05

Values represent mean ± SD.
*$p < 0.01$, compared with nonpregnant state.
†$p < 0.001$, compared with nonpregnant state.
‡$p < 0.05$, compared with nonpregnant state.

Internal carotid artery velocimetry was done with a pulsed Doppler system, TC2-64B (EME, Ueberlingen, Federal Republic of Germany) with a 4 MHz pulsed Doppler transducer. We used a modification of the method of Kirkham et al.,[7] positioning the probe just medial to the sternocleidomastoid muscle at the angle of the submandibular bone (Fig. 1, *B*). Transducer position and sample volume depth were adjusted until the most defined signals were obtained, keeping the angle between insonating beam and blood flow as low as possible. Our device uses a 64-point Fast Fourier Transform spectrum analyzer. The probe is 11 mm in diameter and uses a focused beam operating at depths of 7 to 77 mm electronically adjustable in 2.5 mm increments. Burst width is 2.6 μsec and axial extension 20 mm in the sample volume. We generally used a range of 0 to 100 cm/sec in which the pulse repetition frequency is 10 kHz. The wall thump high-pass filter is approximately 150 Hz and the low-pass filter is 9 kHz. The output is displayed as a time versus Doppler shift plot on a screen and it is stored as printed data.

The patient was placed at a 15-degree angle in a semirecumbent position with eyes open in a silent room during internal carotid artery velocimetry. Sweep speed was 4 seconds per screen with signals from both internal carotid arteries recorded for two screens each. Peak systolic velocities, mean velocities, and pulsatility indexes from each screen were averaged for each side (Fig. 1, *A*). Averages for the two sides were added and averaged again to obtain the final peak systolic velocity, mean velocity, and pulsatility index. Values of side differences were also calculated. The pregnant women were classified into nine groups for every four gestational weeks beginning from week 4. Where appropriate, significant differences were calculated by estimating the multiples of standard deviation and by Student's *t* test.

Results

Table I shows characteristics of the subjects. Each group of pregnant women was statistically similar to nonpregnant women in parity and age. Mean delivery date (±SD) of pregnant women was 39.0 ± 1.4 weeks of gestational age, and mean birth weight was 3044 ± 505 gm.

Values of internal carotid artery velocities in nonpregnant and pregnant women are shown in Table II and Figs. 2 and 3. Mean values of peak systolic and mean velocity in nonpregnant women were 61.2 ± 8.1 and 38.1 ± 6.3 cm/sec. Until 28 weeks of gestation, values of peak systolic and mean velocity in pregnant women were not statistically different from those of nonpregnant women. After 28 weeks, values of peak systolic and mean velocity fell significantly. In the 36- to 40-week group, peak systolic and mean velocity were 49.3 ± 8.7 and 28.4 ± 4.6 cm/sec, respectively, 19.4% ($p < 0.001$) and 25.5% ($p < 0.001$) less than those in nonpregnant women. Table II and Fig. 4 show pulsatility index in the internal carotid artery. Pulsatility index at 4 to 31 weeks' gestation was significantly higher than that in non-pregnant women. Pulsatility index af-

sociate with candidiasis in our study. On the other hand, the number of episodes of sexual intercourse was inversely related to the occurrence of trichomoniasis and candidiasis, whereas it was unrelated to bacterial vaginosis (Table III).

We consider multiple partners a better indication than number of sexual episodes of a sexual life style that would place a woman at increased risk of acquiring a STD. Thus we believe that our data support the notion that trichomoniasis and bacterial vaginosis are sexually transmitted, despite the observations that trichomoniasis is inversely related and bacterial vaginosis is unrelated to number of sexual episodes. On the other hand, the finding that candidiasis is unrelated to number of sexual partners suggests that sexual transmission is not a major cause of yeast infections among our subjects. The inverse relationship between number of sexual episodes and trichomoniasis and candidiasis may be due to a reduction in sexual episodes because of symptoms of these genital infections in the weeks preceding their diagnosis. A paucity of symptoms of bacterial vaginosis may account for the absence of a similar effect on sexual activity.

The most striking finding of this study is that oral contraception appears to be a strong protective factor against trichomoniasis. The validity of this finding is enhanced by the observations that oral contraceptive use was not significantly associated with bacterial vaginosis and candidiasis (Table IV). Furthermore, Louv et al.[7] reported that oral contraceptive use increased the infection rates for both chlamydia and gonorrhea among these women. It is unlikely that some source of bias or confounding could have affected the results of these different genital infections in opposite directions.

The protective effect of oral contraceptive use on trichomoniasis is supported by a sparse but consistent epidemiologic literature. In a 1979 British case-control study,[15] the relative risk of trichomoniasis was 0.5 (95% confidence interval 0.29 to 0.85) for oral contraceptive users compared with nonusers. In a cross-sectional study of women attending a STD clinic in the United Kingdom,[16] the relative prevalence of trichomoniasis was 0.67 (95% confidence interval 0.49 to 0.91) for oral contraceptive users compared with nonusers. This latter study controlled for number of sexual partners as a possible confounder. Our study compared oral contraceptive users with women using intrauterine contraceptive devices or those who had had a tubal ligation. Since the association is adjusted for age, race, education, marital status, parity, number of sexual partners, and number of sexual episodes, confounding by these factors should have been eliminated. Furthermore, chance is an unlikely explanation of the finding because of the small p value, and we cannot identify any other plausible explanation of the finding other than causality.

In a recent article it was reported that *T. vaginalis* possesses estrogen receptors and that 17β-estradiol increases its growth.[17] Furthermore, the binding of 17β-estradiol was inhibited by the antiestrogen tamoxifen citrate. Since endogenous estrogens enhance the growth of *T. vaginalis*, we speculate that oral contraceptives could compete with them for the same receptors, ultimately protecting from *T. vaginalis* infection. Oral contraceptives also could modify the characteristics of the cervical mucosa and reduce the ability of *T. vaginalis* to infect it.

In summary, we found a strong protective effect of oral contraceptive use against trichomoniasis and a weak, statistically nonsignificant, protective effect of spermicide use on trichomoniasis and bacterial vaginosis. Multiple sexual partners was a risk factor for trichomoniasis and bacterial vaginosis but not for candidiasis.

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Pregnant women		
28-31 wk (n = 8)	*32-35 wk (n = 7)*	*36-40 wk (n = 16)*
29.3* ± 5.0 2.5	30.0* ± 5.4 5.7	28.4† ± 4.6 4.6
52.5‡ ± 6.8 4.3	51.2* ± 7.5 10.3	49.3† ± 8.7 9.8
0.99† ± 0.12 0.03	0.91 ± 0.15 0.07	0.83 ± 0.12 0.05

ter 32 weeks returned to the nonpregnant value. Values of mean velocity, peak systolic, and pulsatility index showed no laterality between right and left sides at any stage of gestation.

Comment

Whether cerebral blood flow can be estimated by internal carotid artery velocimetry is debatable. In 1980 Risberg and Smith[5] reported a high correlation between values of internal carotid artery velocimetry and those of cerebral blood flow by the xenon 133 inhalation technique. They found a correlation coefficient of 0.88 ($p < 0.001$) between right hemispheric blood flow and internal carotid end-diastolic velocity in the right side, and 0.83 ($p < 0.001$) in the left side.

When the values of internal carotid artery velocimetry are interpreted as an index of cerebral blood flow, several factors must be considered. Velocity, not flow, was measured. Because no precise noninvasive methods are available, we did not measure arterial diameter. The fact that excellent correlation between the values of internal carotid artery velocity and hemispheric cerebral blood flow was demonstrated in the study by Risberg and Smith[5] without regard to arterial diameter suggests that our data reflect actual cerebral blood flow. It is not likely that the diameter of a large artery such as the internal carotid artery changes during pregnancy.

The angle between ultrasound beam and vessel must be kept constant among cases because velocity values are in part dependent on the angle. In this study we attempted to keep the insonating angle as parallel to the vessels as possible, however, zero degrees could not be obtained because of the anatomic position of the internal carotid artery. If the angle between the blood velocity vector and the beam is less than 20 degrees, variations in velocity are mathematically determined to be less than 6%. In our study, in which the same examiner performed all measurements, variation in angle between the vessel and insonating beam was believed to be less than 20 degrees.

The brain is supplied by two primary blood flows, the carotid and the vertebrobasilar systems. Measurement of carotid velocity alone does not completely assess the entire brain blood supply. Contribution of the vertebrobasilar system was estimated to be approximately 10% by Hardesty et al.,[6] but its extent remains controversial.

Although the factors previously described may be a source of error when cerebral blood flow is assessed by internal carotid artery velocimetry, this method is the most suitable for the study of cerebral hemodynamics in pregnant women because of its noninvasive, simple, and instantaneous character.

There are no reports of serial changes in maternal cerebral circulation. Cerebral blood flow in pregnant women was described by McCall[1] in 1949 in a study of nine normal young women between 34 and 40 weeks' gestation and 29 patients with toxemia of pregnancy using Ketty and Schmitt's nitrous oxide method. Cerebral blood flow in late pregnancy was much the same as that in normal young adult men. These results seem incompatible with our results. The earlier study was unsatisfactory because values of pregnant women were not compared with those of nonpregnant women but with those of men.

Two recent investigations have shown that cerebral blood flow in women is greater than that in men. Grolimund and Seiler[7] performed internal carotid artery velocimetry with the same techniques as ours except that they used pulsed 2 MHz frequency ultrasonographic Doppler rather than 4 MHz. They demonstrated that the mean (±SD) velocity of the internal carotid artery in women (mean age, 55.6 years) was 39.2 ± 9.3 cm/sec and statistically greater than that in men (mean age, 55.4 years), 34.3 ± 7.5 cm/sec ($p < 0.00005$). They speculated that the difference of mean velocity values between men and women was partially a result of the lower hematocrit of women, which reduces viscosity of blood and thus increases cerebral blood flow. Devous et al.[8] measured regional cerebral blood flow in 97 normal subjects (56 men, 41 women) quantitatively with the inert gas washout technique with xenon 133 and single-photon emission computed tomography. They found that regional cerebral blood flow in women was higher than in men at all ages with statistical significance in the 20- to 29-year old ($p = 0.01$) and 30- to 39-year-old ($p = 0.03$) groups.

Bacterial vaginosis: Diagnostic and pathogenetic findings during topical clindamycin therapy

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We examined subjective and objective correlates among 67 women with symptomatic bacterial vaginosis before and after treatment with intravaginal clindamycin or placebo. We found no preponderance of any sexual practices among these patients. Nine patients (13.4%) had had hysterectomy. Whereas odor and discharge were the most common symptoms, 30 patients (44.8%) also complained of vulvovaginal irritation. Symptoms correlated poorly with objective therapeutic outcome. On examination the diagnosis would have been missed in seven patients (10.4%) if the clinician relied on presence of an abnormal vaginal discharge to suggest bacterial vaginosis. Vaginal pH >4.5 was found immediately after curative therapy in 59.6% of patients. *Mobiluncus* spp. morphotypes were 99.0% specific and 52.1% sensitive and proline aminopeptidase activity in vaginal fluid was 84.4% sensitive and 70.2% specific for diagnosis. Our Gram stain criteria yielded no false-negative results, 6.1% false-positive, and frequent indeterminate results after therapy. We found little evidence for sexual transmission of bacterial vaginosis. Recurrence after effective therapy was not predicted by vaginal pH elevation, positive or indeterminate Gram stain result, or positive proline aminopeptidase test. (Am J Obstet Gynecol 1990;163:515-20.)

Key words: Bacterial vaginosis, vaginitis, sexually transmissible disease, proline aminopeptidase, *Mobiluncus* spp.

There have been important evolutionary steps in our understanding of bacterial vaginosis since it was described under the name of *Haemophilus vaginalis* vaginitis by Gardner and Dukes in 1955.[1] New laboratory diagnostic tests of vaginal fluid have been developed, including Gram stain,[2] gas-liquid chromatography,[3] and proline aminopeptidase testing.[4] Clinicians have come to understand that the involvement of *Haemophilus* (now *Gardnerella*) *vaginalis* may be incidental, and that the characterization of this condition is replacement of *Lactobacillus* spp. by various anaerobic bacteria as the dominant vaginal flora.[3, 5] Although clearly associated with bacterial vaginosis, the role of *Mobiluncus* spp. remains uncertain.[6]

The cause of bacterial vaginosis is not known, nor is the reason for frequent recurrences in some women. Some studies have suggested that it is a sexually transmitted disease,[5, 7] but other studies have not found evidence for such a cause.[8-10] Whether various components of the diagnosis, for example the relative alkalinity of vaginal fluid, represent cause or effect is not known. Although bacterial vaginosis is found in 50% of women with an intrauterine contraceptive device in situ[7] and in 86% of those with vaginal trichomoniasis,[11] it is also found commonly in their absence. The common thread(s) that results in bacterial vaginosis among these women has not been identified.

The signs and symptoms of bacterial vaginosis are variable and often subtle; up to 50% of some affected patient groups are asymptomatic.[9] Thus, although current data suggest that this process may be involved in important upper genital tract complications in pregnant[12] and nonpregnant women,[13, 14] the diagnosis of bacterial vaginosis may not be suspected with appropriate frequency until clinicians are afforded an adequate understanding of its presentation.

In a recent study of the use of topical clindamycin in the treatment of bacterial vaginosis, we gathered data to attempt to elucidate some of these issues regarding the clinical presentation, diagnosis, and pathogenesis of this disease.

Material and methods

Women with any vaginal symptoms seen in the gynecology clinics of the two centers that conducted this study were evaluated for the presence of bacterial vaginosis. The following conditions excluded patients from participation in this study: age less than 18 or greater than 45 years, allergy to clindamycin, premenarchal or postmenopausal, pregnancy or lactation, use of any systemic or intravaginal antibacterial agents dur-

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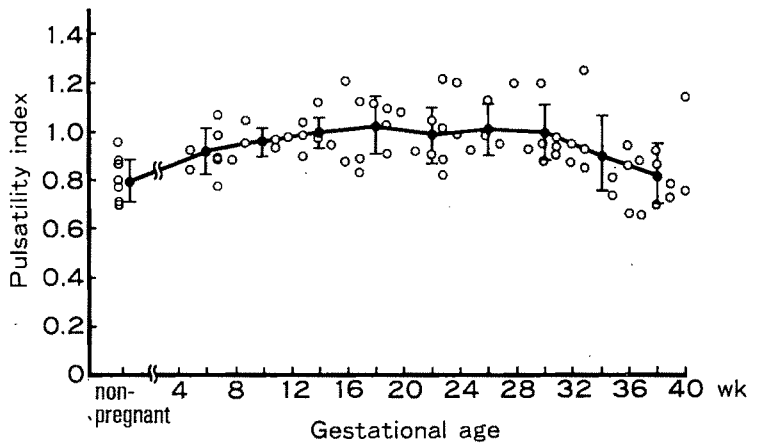


Fig. 4. Pulsatility index in internal carotid artery in nonpregnant women and women with uncomplicated pregnancies. *Open circles* indicate mean values of right and left carotid arteries. *Bars* represent mean ± SD.

Considering the predominance of cerebral blood flow in women, the studies by McCall[1] indicate that the high flow level in nonpregnant women becomes a low flow level in late pregnancy because it is then equal to the flow level in men. This is in agreement with our results.

Mean velocities in the internal carotid artery in the first and second trimester were almost equal to those in the nonpregnant state but were reduced by approximately 20% in the third trimester, indicating a reduction in cerebral blood flow. Although the causes of this change are unclear, chemical factors induced by pregnancy, such as hypocapnia and metabolic acidosis, or physical factors, such as increased cardiac output in pregnancy, or both, appear to affect cerebral hemodynamics. Increased pulsatility index values between 4 to 31 weeks' gestation may be caused by increment of stroke volume rather than increase of cerebrovascular resistance, because pulsatility index not only represents downstream vascular resistance of the cerebral vascular beds but also variables upstream from the point of measurement, such as cardiac output and stroke volume.[9] It is interesting to note that velocity in the internal carotid artery decreases during the third trimester of pregnancy when incidence of cerebral arterial occlusion is higher than during other trimesters.[2]

Doppler velocimetry of the internal carotid artery was found to be highly useful in studying cerebrohemodynamics in pregnancy. More investigation is needed to explain factors responsible for changes in cerebral circulation in pregnancy.

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ing the 2 weeks before enrollment, history of antibiotic-associated colitis or frequent diarrhea, requirement for other ongoing antibiotic therapy, an intrauterine contraceptive device in place, previous entry into this study, the presence of mucopurulent cervicitis, vaginal candidiasis, herpes genitalis, or trichomoniasis, presently menstruating, or Gram stain of vaginal secretions not consistent with bacterial vaginosis.

Patients who were not excluded who were determined to have bacterial vaginosis and who gave written informed consent to participate were entered into the study. Bacterial vaginosis was defined as follows: the presence of clue cells on wet-mount slide (vaginal secretions mixed with saline solution and examined by high-dry microscopy) plus at least two of the following conditions: (1) vaginal discharge pH >4.5, (2) an increased thin homogeneous vaginal discharge, (3) release of a fishy (amine) odor from a sample of the discharge after addition of 10% potassium hydroxide (sniff test). A clue cell was defined as a squamous epithelial cell so heavily studded with bacterial forms that the cell border was obscured.

Vaginal Gram stains were classified according to a modification of the criteria of Spiegel et al.[2] as follows: consistent with bacterial vaginosis—predominating and large numbers (3+ to 4+) of mixed bacterial types including *Gardnerella* morphotype and other gram-positive or gram-negative rods or cocci or both, with *Lactobacillus* morphotype in the minority or absent among total vaginal flora and fungal forms absent; normal—Lactobacillus morphotype clearly predominant among total vaginal flora, with or without *Gardnerella* morphotypes, and fungal forms absent; indeterminate—those cases meeting criteria for neither normal nor consistent with bacterial vaginosis. During Gram stain evaluation the presence or absence of curved rods morphologically consistent with *Mobiluncus* spp. was recorded.

When eligibility for study enrollment was thus confirmed, patients were interviewed to gather epidemiologic data, genital tract symptoms, and medical and sexual history. During pelvic examination vaginal discharge was collected from the anterior and lateral fornices for pH testing, wet-mount microscopic examination in saline solution and potassium hydroxide, sniff test, Gram stain, proline aminopeptidase testing,[4] and culture for fungi, trichomonads, and herpes virus. Endocervical swabbings were obtained to rule out the presence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Patients were then provided in a double-blind fashion with either clindamycin phosphate cream at a concentration of 0.1%, 1.0%, or 2.0% or placebo cream (respective pH 6.0, 5.7, 5.4, 6.2) for vaginal administration, 5 gm twice daily for 5 days. They were instructed to use condoms during intercourse and to refrain from use of any other vaginal agents and systemic antimicrobial therapy.

Patients were seen for outcome evaluation at 4 to 7 days and again at 1 month after completion of therapy and classified as follows. Cure was defined by absence of clue cells (i.e., normal squamous cells) in vaginal fluid on wet mount plus presence of at least two of the following three: (1) grossly normal vaginal discharge (defined as translucent white, flocculent, low volume), (2) vaginal pH ≤4.5 , and (3) negative sniff test. If criteria for cure were not met, the case was declared a therapeutic failure. Nonevaluable patients were those patients who used fewer than eight doses of medication on schedule, failed to return for the first follow-up visit, had a positive test for another lower genital tract pathogen from the enrollment visit, or used any other intravaginal or systemic antibacterial agent before the first return visit. Cases that were declared therapeutic failures were offered therapy with open-label 1% clindamycin cream and were reevaluated as in the blinded therapy protocol.

Therapeutic results[15] did not differ significantly as a function of clindamycin concentration in the creams; 43 of 46 patients (93%) and 35 of 39 (90%) were cured 1 week and 1 month, respectively, after active drug therapy compared with four of 16 (25%) and three of four after placebo therapy. When open-label treatment results are included, the cure rates were 56 of 61 (92%) and 37 of 44 (84%) 1 week and 1 month after active drug therapy.

Statistical techniques used for data analysis were χ^2 test, Fisher's exact test, or the randomization test as appropriate.

Results

Sixty-seven symptomatic patients with pure (all cultures for other lower genital pathogens were negative) bacterial vaginosis were enrolled. Their epidemiologic characteristics are presented in Table I. Further examination of these patients with pure bacterial vaginosis who supplied sexual history (N = 66), reveals that 33 (50.0%) participated in oral-vaginal sex before onset of bacterial vaginosis symptoms, and 2 of 33 (6.1%) discontinued this practice after onset of those symptoms; 3 of 66 (4.5%) related onset of symptoms to initiation of oral-vaginal sex. A history of penile-anal intercourse was found in only two patients (3.0%). Four (6.1%) patients related onset of symptoms to initiation of penile-vaginal sex or a new sexual partner. Genital symptoms in current sexual partners were described by eight of the 67 (11.9%) patients with pure bacterial vaginosis, penile dermatitis symptoms in five, and urethritis symptoms in three. Other genital tract disease was present in seven patients among those with pure bacterial vaginosis (endometriosis in five patients, hy-

Changes in active and latent collagenase in human placenta around the time of parturition

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High levels of collagenase are present in cervical extracts and in the circulation in women at parturition. This study examines the content of collagenase in human placentas at term, the possible contribution to circulating enzyme, and the changes that occur at parturition. Active and latent forms of collagenase are detectable in placentas with apparent relative molecular mass of 60,000 and 65,000 d, respectively. Gel-filtration chromatography was used to identify the presence of excess tissue inhibitor of metalloproteinase as the major collagenase inhibitor in the extracellular matrix of human placentas. After the onset of labor, there was a significant increase in total collagenase activity. Inactivation of the tissue inhibitor of metalloproteinase by reduction of placental extracts with dithiothreitol and alkylation with iodoacetamide resulted in a twelvefold to seventeenfold increase in collagenase activity. Umbilical cord collagenase levels were significantly lower than those in maternal circulation. The possibility of circulating collagenase originating from placenta in labor is discussed. (Am J Obstet Gynecol 1990;163:499-505.)

Key words: Human placenta, collagenase, tissue inhibitor of metalloproteinase, parturition

Human placenta plays a central role in the growth and development of the fetus. In addition to controlling the vital functions of nutrition and respiratory gas exchange to the fetus, it is involved in the biosynthesis of steroid and peptide hormones and growth factors.[1] This complx organ is also of interest because it is a rich source of collagen. The fibrillar collagen types I and III account for >90% of the total placental collagen at term; the remaining collagen is mainly types IV and V.[2] When human placenta synthesizes collagen in organ culture approximately two thirds of the collagenous proteins produced are of types I and III.[3] Several reports indicate that the placenta is rich in cysteine proteinases such as cathepsin B, collagenolytic cathepsin, and calcium-activated neutral proteinases.[4-7] These cysteine proteinases participate in the degradation of intracellular and extracellular matrix proteins. The presence of cysteine proteinase inhibitors in human placenta[8] supports a regulatory function for these proteases.

Although cysteine proteinases are capable of degrading telopeptide ends of fibrillar collagen, the process of collagenolysis cannot occur at physiologic pH without cleavage of the collagen triple helix by collagenase. We have previously shown that extracts of human placenta at term contain collagenase[9] and that collagenase is implicated in the mechanism of dilatation of the uterine cervix in women at parturition.[10] High levels of collagenase were present in cervical extracts and in serum at delivery.[9, 10] The source of serum collagenase in women has not been identified. One may speculate that enzymatic degradation of placental collagen and other components of the extracellular matrix becomes important near parturition when the placenta must separate from the uterine wall.

This study was undertaken to optimize detection of collagenase in human placenta and to investigate possible changes in the activity of this enzyme at parturition. The relationship between collagenase in maternal and fetal compartments was also determined.

Material and methods

Material. Chemical reagents were obtained from the following sources: [^{3}H]acetic anhydride (50 mCi/mmol) and Aquasol scintillation fluid (New England Nuclear, Boston); bovine trypsin (crystallized × 3, 180 U/mg, Worthington Enzymes, Freehold, N.J.); bovine chymotrypsin (crystallized × 3, 153 U/mg), ethylenediaminetetraacetic acid, 1,10-phenanthroline, and Brij 35 (polyoxyethylene 23 lauryl ether, Sigma Chemical Company, St. Louis); aminophenylmercuric acetate (practical grade, ICN-K + K Laboratories, Plainview, N.Y.). Polypropylene Chemtube containers were purchased from Bio-Rad Laboratories (Richmond, Calif.).

Tissue specimens. Human placentas were obtained

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Table I. Selected characteristics of patients with bacterial vaginosis

	All patients with pure bacterial vaginosis (N = 67)*
Age (yr)	29†
Weight (lb)	152
Unmarried (*n*)	48 (71.6%)
Parity	1.6
Duration of symptoms (days)	269.9
No. of sexual partners last 12 mo	1.4
History of any sexually transmitted disease (*n*)	27 (40.3%)
History of vulvovaginal candidiasis (*n*)	11 (16.4%)
No. episodes coitus last 30 days	6.7
Contraception (*n*)	
Combined oral contraceptives	18
Condom	15
Tubal sterilization	10
Hysterectomy	9
None	6
Abstinence	4
Diaphragm	3
Depotmedroxyprogesterone	1
Danazol	1

*Patients meeting criteria for diagnosis of bacterial vaginosis in whom testing showed no other lower genital tract infection.

†All values are mean for the group unless otherwise indicated.

Table II. Symptoms among all patients with pure bacterial vaginosis ($N = 67$)

Symptom complex	*n*	*Frequency (%)*
Odor + discharge	22	33.8
Odor + discharge + irritative symptoms*	18	26.8
Discharge only	13	19.4
Odor only	3	4.5
Discharge + irritative symptoms	3	4.5
Odor + irritative symptoms	2	3.0
Odor + discharge + irritative + urinary symptoms†	2	3.0
Odor + discharge + irritative + abnormal vaginal bleeding	2	3.0
Irritative symptoms only	1	1.5
Discharge + irritative + abnormal vaginal bleeding	1	1.5

*Irritative symptoms: any among vulvovaginal pruritus, pain, burning, and frictional dyspareunia.

†Urinary symptoms: any among dysuria, urgency, and frequency.

Table III. Examination findings at study entry among patients with pure bacterial vaginosis ($N = 67$)

Finding	*n*	*%*
Vulvar inflammation*	8	11.9
Vaginal inflammation	10	14.9
Cervical inflammation	7	10.4
Any of vulvar, vaginal, or cervical inflammation	20	29.9
Vulvar fissures	1	1.5
Vaginal discharge on vulva	43	64.2
Uterine, adnexal tenderness	9	13.4
Increased thin homogenous vaginal discharge	60	89.6
Vaginal pH >4.5	64	95.5
Positive sniff test	62	92.5

*Inflammation: any of erythema, edema, tenderness.

poplastic vulvar dystrophy in one, and anovulation in one).

Table II expresses the frequency of symptom constellations among the 67 patients with pure bacterial vaginosis; symptoms were assessed only categorically, not quantitatively. When individual symptoms are examined with or without other symptoms, vaginal discharge is found in 61 (91.9%), followed by vaginal odor in 49 (73.1%), irritative symptoms in 30 (44.8%), and 3 (4.5%) each with complaints of abnormal bleeding and urinary symptoms.

Table III shows the examination findings at the time of entry into the study for all 67 patients with pure bacterial vaginosis. Inflammatory changes on examination were found in 20 of 67 (29.9%) patients with pure bacterial vaginosis, comparable to the frequency of symptoms of vulvovaginal irritation reported. All criteria for diagnosis were present in 52 of 67 (77.6%) patients, whereas seven (10.4%) lacked the characteristic discharge, five (7.5%) lacked the positive sniff test, and three (4.5%) had a vaginal pH ≤4.5.

Curved rods resembling *Mobiluncus* spp. were found in 36 of the 67 patients (53.7%). Proline aminopeptidase activity in vaginal fluid from patients with pure bacterial vaginosis was positive in 27 of 34 (79.4%). Proline aminopeptidase activity was positive in 25 of 30 (83.3%) patients with all criteria for bacterial vaginosis present, both of two patients who lacked the positive potassium hydroxide sniff test, and neither of two with vaginal pH was ≤4.5. Sixteen of 18 (88.9%) patients with and 11 of 16 (68.8%) patients without curved rods on vaginal smear were positive for proline aminopeptidase activity ($p > 0.05$ for all comparisons).

Analysis of the relationships between patients' symptoms and presence of objective criteria for the diagnosis of bacterial vaginosis after treatment revealed a poor correlation. Resolution of all vulvovaginal symptoms did occur more frequently among patients cured by objective criteria after blinded treatment (29 of 47, 61.7%), but not significantly more frequently than among patients with persistent disease by objective cri-

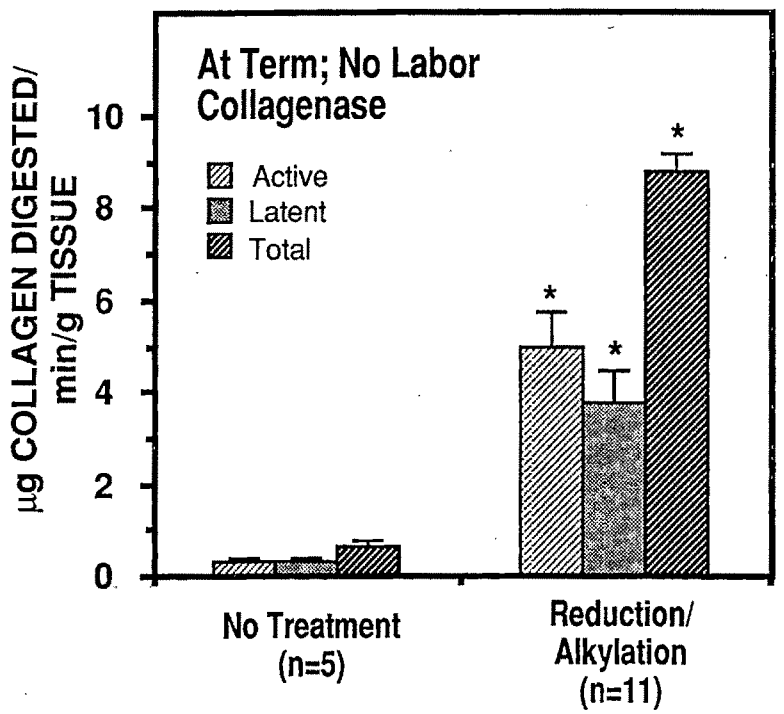


Fig. 1. Active, latent, and total collagenase in human placenta at term (37 to 42 weeks), not in labor (mean ± SEM). There is a twelvefold to seventeenfold increase in collagenase activity after inactivation of tissue inhibitor of metalloproteinase by reduction with dithiothreitol and alkylation with iodoacetamide; *n* refers to numbers of placentas tested. *Asterisk* denotes $p < 0.001$ for the difference between active, latent, and total collagenase levels before and after reduction-alkylation.

immediately at delivery according to a protocol approved by the local human research committee at the University of Miami. Tissue was taken from those cesarean sections performed at term (37 to 42 weeks) for standard indications from two groups of women with normal gestation. One group was in labor with the cervix dilated 4 to 8 cm and the other group was not in labor and the cervix was closed (0 to 2 cm). Approximately 10 gm of tissue was excised across the fetal and maternal sides of the placenta. The membranes and major vessels were removed. The tissue specimens were washed in ice-cold normal saline solution, frozen at −20° C overnight, and stored at −70° C. Specimens were thawed at room temperature immediately before extraction of collagenase for assay.

Preparation of collagenase substrate. Acid-soluble collagen was purified from the skins of adult female rats (Sprague Dawley, Charles River Breeding Laboratories, Wilmington, Mass., 225 to 275 gm) as described.[11] Briefly, collagen was extracted in 0.5 mol/L acetic acid at 4° C and precipitated by 1.7 mol/L sodium chloride. After two cycles of redissolving and reprecipitating, the precipitate was dissolved (1.5 to 2.0 mg/ml) in buffered 2 mol/L urea and dialyzed. This product is referred to as intact collagen. Intact collagen was then acetylated with tritiated acetic anhydride.[12] The telopeptide ends of this labeled collagen were removed by pepsin digestion.[13] Labeled telopeptide-free collagen was purified and sodium dodecyl sulfate–gel electrophoresis was used to evaluate the completeness of the pepsinization as described.[11] The final product contained approximately 6.4×10^6 cpm/mg collagen.

Preparation of collagenase

Serum samples. Blood samples were obtained from mothers and umbilical cords immediately at delivery. Samples were collected in plain tubes and allowed to clot at room temperature for 30 minutes. They were then chilled and centrifuged for 15 minutes at 1500 rpm (750 *g*) at 4° C. The serum was withdrawn to within 1 cm of the clot to avoid contamination with leukocytes and frozen at −20° C until assayed. Samples were thawed at room temperature immediately before processing for collagenase assay. The α_2-macroglobulin was inactivated by dialyzing serum versus 3 mol/L potassium thiocyanate in 50 mmol/L Tris–hydrochloric acid and 10 mmol/L calcium chloride, pH 7.5, for 6 hours at 4° C and then against 100 volumes of assay buffer for 18 hours.[14] The assay buffer consisted of 50 mmol/L Tris–hydrochloric acid, 200 mmol/L sodium chloride, 10 mmol/L calcium chloride, 0.05% Brij 35, and 0.02% sodium azide, all adjusted to pH 7.5.

Table IV. Status at second return visit 1 Month after therapy for bacterial vaginosis as a Function of qualifiers of cure at first return visit 4 to 7 days after treatment

Status at first return visit	*n**	*Status at second return visit*			
				Examination normal except	
		Normal†	*Recurrent bacterial vaginosis*	*Vaginal pH >4.5*	*Discharge of bacterial vaginosis*
Unqualified cure	13	8 (61.5%)	1 (7.7%)	4 (30.8%)	0
Cure with pH >4.5	27	18 (66.7%)	3 (11.1%)	5 (18.5%)	1 (3.7%)
Cure with positive potassium hydroxide sniff test	1	1	0	0	0
Cure with candidiasis	2	0	1	1	0
TOTAL	43	27 (62.8%)	5 (11.6%)	10 (23.3%)	1 (2.3%)

*Only those patients for whom second return visit data are available are included.
†No criteria for diagnosis of bacterial vaginosis present.

Table V. Correlation of laboratory parameters with presence or absence of bacterial vaginosis by clinical criteria relative to intravaginal clindamycin or placebo treatment, including visits after blinded and open-label regimens

Parameter	*Result*	*Entry visit: Bacterial vaginosis*		*4-7 days after completion of treatment: Bacterial vaginosis*		*1 mo after completing treatment: Bacterial vaginosis*		*Cumulative: Bacterial vaginosis*	
		Present	*Absent*	*Present*	*Absent*	*Present*	*Absent*	*Present*	*Absent*
Gram stain	Consistent with Bacterial vaginosis	67(100%)*	—	14(82.4%)	4(6.7%)	9(100%)	2(5.3%)	23(88.5%)	6(6.1%)
	Indetermiante	0	—	3(17.6%)	46(76.7%)	0	11(28.9%)	3(11.5%)	57(58.2%)
	Normal	0	—	0	10(16.7%)	0	25(65.8%)	0	35(35.7%)
Proline aminopeptidase activity	Positive	27(79.4%)	—	5(100%)	9(34.6%)	6(100%)	5(23.8%)	38(84.4%)	14(29.8%)
	Negative	7(20.6%)	—	0	17(65.4%)	0	16(76.2%)	7(15.6%)	33(70.2%)
Curved rods	Present	36(53.7%)	—	9(52.9%)	0	4(40.0%)	1(2.6%)	49(52.1%)	1(1.0%)
	Absent	31(46.3%)	—	8(47.1%)	59(100%)	6(60.0%)	37(97.4%)	45(47.9%)	96(99.0%)

*All patients entering the study were required to have a vaginal Gram stain consistent with bacterial vaginosis. Data in this category are not entered in the cumulative Gram stain data.

teria (6 of 15, 40.0%). Odor and discharge symptoms were resolved in 34 of 47 (72.3%) and 6 of 15 (40.0%), respectively ($p > 0.05$). At the second return visit all symptoms were resolved in 27 of 33 (81.8%) patients with durable cure and in 3 of 5 with recurrent bacterial vaginosis; odor and discharge were resolved in 29 of 33 (87.9%) and 3 of 5, respectively. Similarly, no significant association was found between any of the objective diagnostic criteria and a given symptom.

Among the 47 patients who met criteria for cure at 4 to 7 days after blinded therapy, 28 (59.6%) had persistent elevation of vaginal pH >4.5, one (2.1%) retained a positive sniff test, and none had persistence of discharge consistent with bacterial vaginosis. Table IV shows the relationships between status at the first and second return visits for patients who were initially cured and attended both visits. Recurrence of bacterial vaginosis was equally likely among any of the cure groups as classified at the first return visit.

There were four patients declared cured by our criteria at the first return visit whose vaginal Gram stain remained consistent with bacterial vaginosis; at the second return visit two of them were unqualified cures and two had recurrent disease. Among nine patients who retained positive proline aminopeptidase activity despite clinical cure at the first return visit, at the second return visit seven of eight showed durable cure; four were completely normal, and one each had vaginal candidiasis, pH >4.5, and candidiasis plus pH >4.5.

Durability of cure relative to exposure to male sexual secretions was also examined. Among five patients cured by blinded treatment at the first return visit who

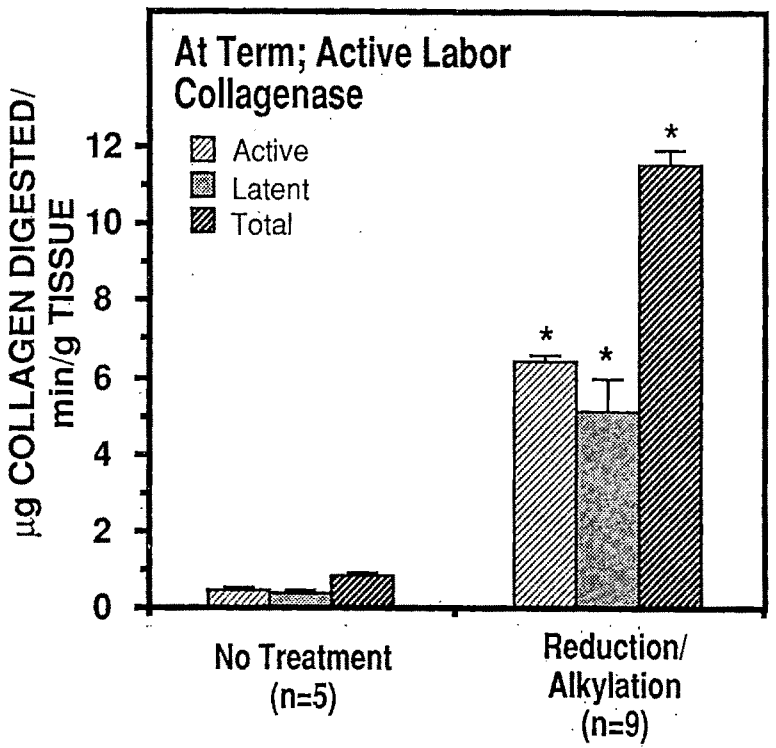


Fig. 2. Active, latent, and total collagenase in human placenta at term (37 to 42 weeks), in active labor (mean ± SEM). There is a thirteenfold to fourteenfold increase in collagenase activity after inactivation of tissue inhibitor of metalloproteinase by reduction with dithiothreitol and alkylation with iodoacetamide; *n* refers to number of placentas tested. *Asterisk* denotes $p < 0.001$ for the difference between active, latent, and total collagenase levels before and after reduction-alkylation.

Placental samples. Collagenase was extracted from placental specimens according to the method of Sellers and Woessner.[15] First the tissue was homogenized in 10 volumes 0.1% Triton X-100 and 10 mmol/L calcium chloride, then the residual tissue was further extracted in 100 mmol/L calcium chloride in 50 mmol/L Tris–hydrochloric acid buffer, pH 7.5, at 60° C for 4 minutes to yield a heat extract. The Triton extract and the heat extract were then dialyzed against assay buffer overnight. Aliquots were removed for enzyme assay and the remainder was stored at −20° C.

Collagenase assay method. Collagenase assay was done according to the method of Dean and Woessner.[11] Enzyme samples (12.5 μl serum, 20 to 100 μl placental extract) were incubated in polypropylene tubes with 35 μg of [^{3}H]telopeptide-free collagen. Aminophenylmercuric acetate (0.5 mmol/L) was added to activate latent collagenase and 1,10-phenanthroline (1 mmol/L) was added for blanks. The total volume was adjusted to 110 μl with assay buffer. Incubation was for 20 hours at 30° C. The reaction was stopped by adding ethylenediaminetetraacetic acid to a final concentration of 40 mmol/L. Acid-soluble intact collagen (200 μg) was added as carrier with 35 μg chymotrypsin and 35 μg trypsin, and the mixture was incubated at 30° C for 90 minutes to digest the products of collagenase action. The undigested [^{3}H]telopeptide-free collagen was precipitated by an equal volume of ice-cold 20% trichloroacetic acid and collected on Millipore AP15-025-00 glass fiber filters (Millipore Corp., Bedford, Mass.), placed into 10 ml Aquasol scintillation fluid, and counted in a Packard Tri-Carb scintillation spectrometer (Packard Instrument Co., Downers Grove, Ill.) (58% efficiency). The percent digestion is calculated as [(Blank − Digest)Blank] × 100. One unit of collagenase is defined as 1 μg [^{3}H]telopeptide-free collagen digested per minute at 30° C. Tissue inhibitor of metalloproteinase was inactivated by reduction of placental extracts with 2 mmol/L dithiothreitol followed by alkylation with 5 mmol/L iodoacetamide.[9, 16] After dialysis against assay buffer, samples were assayed for collagenase as described.

Gel-filtration chromatography. Samples of enzyme extracts (10 ml) were applied to a 1 × 110 cm column of Ultragel ACA-34 equilibrated with assay buffer containing 1 mol sodium chloride. Fractions of 10 ml were collected and dialyzed against assay buffer. Fractions were assayed with and without aminophenylmercuric acetate to determine the positions of latent and active collagenase, respectively. Molecular weights were estimated on the basis of protein markers chromatographed under identical conditions.

had recurrent bacterial vaginosis at the second return visit, all had been exposed (had had intercourse without condoms); 19 of 38 (50%) patients with durable cure had been exposed ($p = 0.06$). When participants in the open-label treatment protocol are included, 6 of 8 (75.0%) with recurrent disease and 21 of 40 (52.5%) with durable cure had been exposed ($p = 0.44$).

Relationships between the laboratory tests we evaluated and our clinical criteria for diagnosis of bacterial vaginosis were examined at each visit and are shown in Table V. The total numbers at each return visit exceed those at the entry visit in this table because all evaluations after blinded, open-label, and placebo therapy are included.

Comment

Although abnormal discharge (91.0%) and vaginal odor (73.1%) were the most common presenting symptoms, two thirds of our patients had other symptoms. Almost half (44.8%) of our patients with pure bacterial vaginosis presented with complaints of vulvovaginal irritation and there was objective evidence of it in 29.9%. Amsel et al.[7] found irritative symptoms in 15.9% of their patients, and Taylor et al.[16] found signs of vaginal inflammatory change in 20%. Despite the generally noninflammatory nature of this process, practitioners should not be dissuaded from the diagnosis by such symptoms or signs. Although one study[14] has suggested a causal relationship between bacterial vaginosis and abnormal uterine bleeding, Eschenbach et al.[13] did not identify a correlation between them; the prevalence of abnormal bleeding was very low (4.5%) among our patients with pure bacterial vaginosis. Thus not only are up to half of the patients with bacterial vaginosis reported in the literature asymptomatic, but in our symptomatic study population there is a wide range of complaints (Table II), and symptomatic response to therapy has inadequate correlation with outcome by objective criteria. Consequently, we advise clinicians to use a "test of cure" examination.

We emphasize that at study entry over 10% of our patients were described to have a vaginal discharge that was either physiologic or absent. Because bacterial vaginosis is often asymptomatic and because abnormal discharge is the only one of the four criteria for diagnosis that can be assessed simply during the examination, clinicians may use the presence of an abnormal vaginal discharge as the "trigger" to consider the diagnosis of bacterial vaginosis; this approach will result in missing as many as one in 10 cases.

A significantly higher frequency of adnexal tenderness (4%) and a diagnosis of pelvic inflammatory disease (3%) has been described for patients with bacterial vaginosis.[13] We found uterine or adnexal tenderness or both, in 10 of our 67 (14.9%) patients with pure bacterial vaginosis, three of whom had had hysterectomy; none of these patients was considered to have pelvic inflammatory disease, which would have excluded them from the study. Among those with the uterus in place who returned for follow-up, tenderness had resolved in four of four immediately after curative treatment for bacterial vaginosis and in one of two therapeutic failures. These data suggest that the association between bacterial vaginosis and upper genital tract infection should be pursued.

Other investigators[13] have noted that elevation of vaginal pH is the most sensitive but least specific of the criteria currently used for diagnosis of bacterial vaginosis. In this study the high frequency (59.6%) of persistent vaginal pH >4.5 4 to 7 days after otherwise curative clindamycin treatment negates its diagnostic usefulness in this setting. In addition, increased vaginal pH after otherwise curative treatment did not predict recurrence of bacterial vaginosis within the time frame of this study (Table IV). This finding greatly reduces the likelihood that the original pathogenic event in bacterial vaginosis is relative vaginal alkalinity per se. One month after treatment vaginal pH>4.5 was found in 10 of 38 (26.3%) patients who remained free of bacterial vaginosis, although only five of those 10 were from the group with elevated pH at the first return visit. Whether such lability of vaginal pH is peculiar to a population at persistent risk for bacterial vaginosis cannot be determined from our study.

The frequencies of any contraceptive method other than use of an intrauterine device or any sexual practices, specifically oral-vaginal or penile-anal sex, among our patients with bacterial vaginosis are similar to our general patient population. Most patients were in excellent general health. Clearly, neither cervical mucus nor menstrual flow is required for persistence of bacterial vaginosis since 13.4% of our patients had had hysterectomy.

Our data do not strongly suggest a sexually transmitted cause for bacterial vaginosis. Among our patients we found a relatively low mean number of admitted sexual partners during the preceding 12 months (1.4), a low frequency of genital symptoms in male sexual partners (11.9%), a low rate of recurrent bacterial vaginosis in the absence of treatment of male sexual partners, and no demonstrable difference in recurrence rates as a function of exposure to male genital secretions. Clearly, however, these findings do not conclusively refute sexual transmission, and it should be noted that 71.6% of our patients were unmarried and therefore less likely to be monogamous, and 40.3% gave a history of sexually transmitted disease. It remains possible that our patients had acquired the disease from a remote sexual partner, and that larger numbers of patients may have shown a significantly more frequent

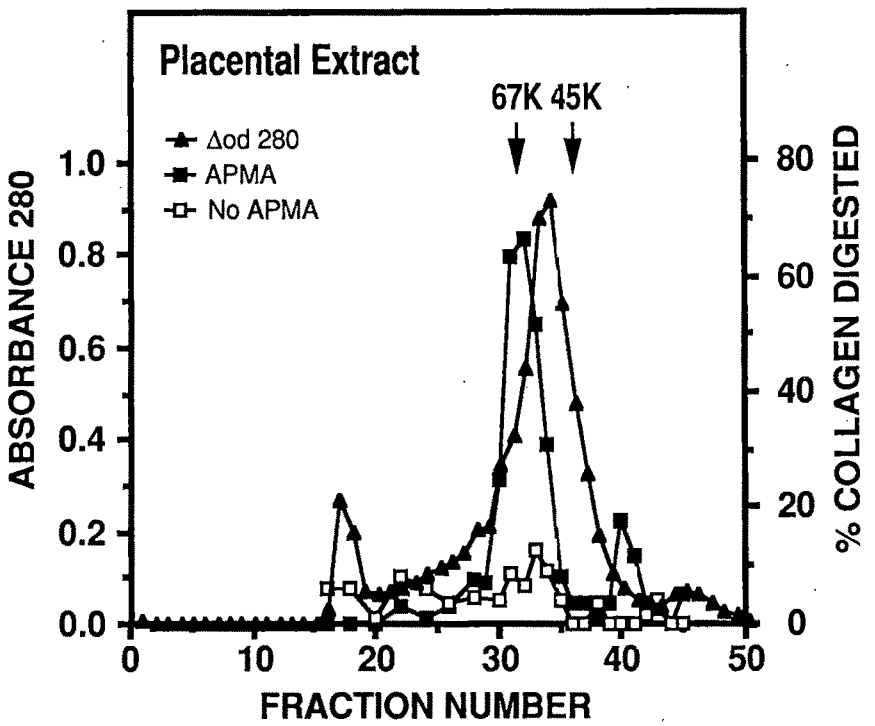


Fig. 3. Gel-filtration chromatography of human placental collagenase (active labor). Heat-extracted collagenase (10 ml) was subjected to gel-filtration chromatography as described in Material and methods section. The absorbance of 280 nm was determined after chromatography. Fractions were dialyzed against assay buffer, and 100 μl aliquots were assayed for collagenase without aminophenylmercuric acetate *(APMA)* (active collagenase) and in the presence of 0.5 mmol/L aminophenylmercuric acetate (latent collagenase). *67 K* and *45 K* refer to elution position of bovine serum albumin and ovalbumin, respectively.

Results

Recovery of collagenase in placental extracts. Collagenase is present in an active form and a latent form. Assay of placental extracts in the absence of aminophenylmercuric acetate detects the active enzyme. Addition of aminophenylmercuric acetate detects the total free (unbound) enzyme present in tissue extracts. The difference between total and active enzyme yields latent enzyme (i.e., that enzyme that cannot be assayed until it is activated). Both the Triton and the heat extracts contained significant amounts of collagenase (approximately one third and two thirds, respectively). Although each fraction was assayed separately, there was no significant change in distribution of collagenase levels in the different extracts before and after labor. Therefore all the data reported are the summation of the two extracts.

Collagenase in human placenta. Assay of dialyzed placental extracts revealed the presence of low collagenase activity. Placentas at term showed mean collagenase levels for active, latent, and total enzyme at 0.29 ± 0.11, 0.32 ± 0.05, and 0.64 ± 0.13 U/gm tissue, respectively (one unit = 1 μg collagen digested per minute at 30° C, mean ± SEM, $n = 5$) (Fig. 1). After spontaneous labor, collagenase levels increased to 0.45 ± 0.11, 0.39 ± 0.1, and 0.84 ± 0.06 U/gm for active, latent, and total collagenase, respectively ($n = 5$) (Fig. 2). The differences were not statistically significant. This low level of collagenase could reflect either a low enzyme concentration, excess inhibitor(s), or both. This issue was resolved by gel-filtration chromatography. The total enzyme activity in crude extracts was greatly increased after chromatography. This indicates that the low levels of collagenase activity were primarily the result of the presence of excess inhibitor(s) that were separated by the chromatography. Presumably the active enzyme and the latent enzyme, after activation by aminophenylmercuric acetate, become bound to inhibitors during the 20-hour assay. The two known inhibitors of collagenase are α_2-macroglobulin and tissue inhibitor of metalloproteinase. Therefore attempts were made to inactivate α_2-macroglobulin by treatment of placental extracts with potassium thiocyanate and to inactivate tissue inhibitor of metalloproteinase by reduction with dithiothreitol and alkylation with iodoacetamide as described in Methods. Inactivation of α_2-macroglobulin did not increase active, latent, or total collagenase in placental extracts (data not

recurrence rate with exposure to semen, as was suggested by the trend seen among patients in the blinded portion of our study.

Our data support the specificity of curved rods (*Mobiluncus* spp. morphotypes) for bacterial vaginosis.[6] In the blinded treatment protocol these organisms were absent among patients cured of bacterial vaginosis by our criteria in 46 of 46 patients at the first return visit and in 36 of 37 at the late visit, and for all data points had an overall specificity in diagnosis of bacterial vaginosis of 99.0% (96 of 97). Among 94 visits of patients with bacterial vaginosis, we identified these organisms in 49 (52.1%). These findings also confirm the susceptibility of *Mobiluncus* spp. to clindamycin as previously reported,[6] and establish the efficacy of topical local treatment.

Using all data points ($N = 92$), we found proline aminopeptidase activity in vaginal fluid to have a sensitivity of 84.4% and specificity of 70.2%. After treatment sensitivity of proline aminopeptidase was 100% (Table V). When this test remains positive after otherwise curative treatment, it does not seem to predict recurrence. However, proline aminopeptidase activity is more sensitive, specific, and practical than gas-liquid chromatographic analysis of vaginal secretions and may emerge as the preferred laboratory test for diagnosis. It is of interest that 10 of 14 (71.4%) false-positive tests occurred in patients with vaginal pH >4.5. We did not find a correlation between the presence of proline aminopeptidase and *Mobiluncus* spp. morphotypes.

We concur with Spiegel et al.[2] with regard to the utility of Gram stain of vaginal fluid in diagnosis of bacterial vaginosis. All of our 67 patients with pure bacterial vaginosis by our clinical criteria at the time of enrollment had confirmatory vaginal Gram stain findings. Although usefulness of Gram stain criteria immediately after therapy was limited by a high frequency of indeterminate results, 1 month after treatment the frequency of indeterminate results decreased. Restoration of a lactobacillus-dominated flora after treatment can be documented by Gram stain classified as normal (Table V). Overall, after treatment the accuracy of a positive result was 79.3% (23 of 29) and of a negative result 100% (35 of 35). It would be useful to compare vaginal Gram stains after systemic metronidazole therapy.

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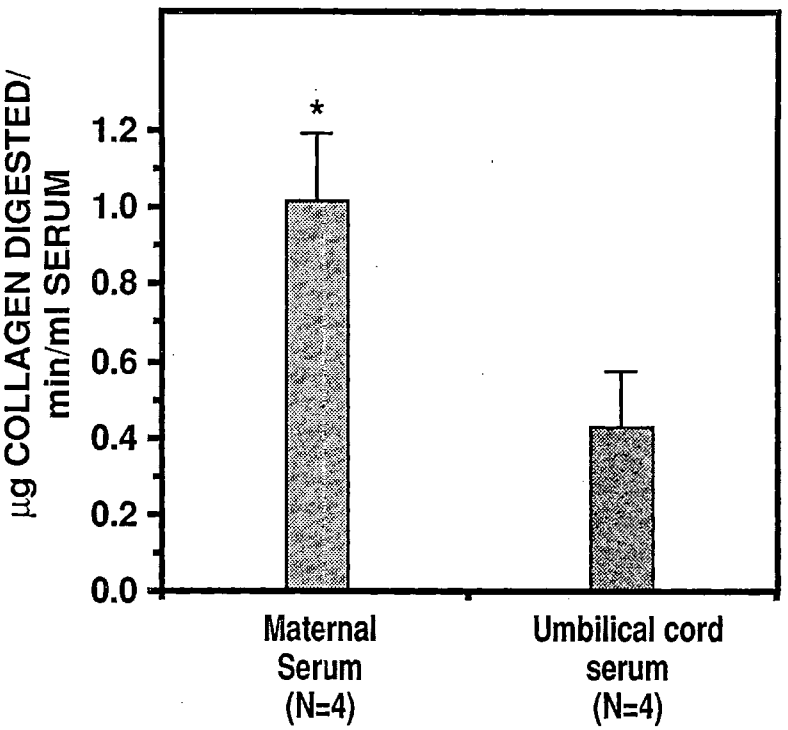


Fig. 4. Distribution of serum collagenase in maternal and neonatal compartments. Collagenase activity was measured in serum after inactivation of α_2-macroglobulin by potassium thiocyanate on paired sera from maternal veins and umbilical cords immediately at delivery (n = four pairs). Maternal serum collagenase levels are higher than umbilical cord serum levels ($p < 0.05$).

shown). Inactivation of tissue inhibitor of metalloproteinase, however, resulted in a marked increase in active, latent, and total collagenase (Figs. 1 and 2). The activity of collagenase recovered was approximately equal to the activity recovered from gel-filtration chromatography. On the basis of this recovery, all placental extracts were reduced and alkylated, dialyzed, and assayed for collagenase. As shown Figs. 1 and 2, placentas at term (in presence or absence of labor) showed a twelvefold to seventeenfold increase in collagenase activity after reduction and alkylation. After the onset of labor there was a statistically significant increase in total enzyme (from 8.76 ± 0.41 to 11.52 ± 0.44 U/gm, $p < 0.01$).

Chromatography of placental collagenase. Extracts of collagenase were chromatographed on an Ultrogel AcA-34 column (LKB Instruments, Rockville, Md.) as described in Methods. Dialyzed fractions were assayed for collagenase in the presence or absence of aminophenylmercuric acetate. The latent form of collagenase had an apparent relative molecular mass of 65,000 d (Fig. 3). The apparent relative molecular mass of spontaneously active enzyme was slightly lower than that of the latent form at 60,000 d.

Maternal-fetal serum collagenase. Fig. 4 represents collagenase activity in maternal and umbilical cord serum taken simultaneously at delivery. Umbilical cord serum levels were lower than those in maternal circulation.

Comment

This study reports the detection of collagenase in human placenta at term and on optimization of detection of the extracted enzyme. The increased recovery of collagenase activity after gel-filtration chromatography was found to be caused by the presence of excess tissue inhibitor of metalloproteinase. Tissue inhibitor of metalloproteinase is the major inhibitor of collagenase and other metalloproteinases in the extracellular matrix of many human tissues. It inhibits collagenase in a 1:1 stoichiometric ratio. It contains disulfide bridges that are essential for activity. Free tissue inhibitor of metalloproteinase is completely inactivated by reduction and alkylation as described under Methods (for review see Stricklin and Welgus[17] and Stricklin[18]). Our results indicate that tissue inhibitor of metalloproteinase is also the major collagenase inhibitor in human placenta. Since potassium thiocyanate treatment of placental extracts did not increase collagenase activity, it is unlikely that α_2-macroglobulin plays a significant role in controlling collagenolysis in the extracellular matrix of human placenta. This is in agreement with the fact that α_2-macroglobulin is mainly present in the circulation and its large size (apparent relative molecular

The relationship of cocaine use to syphilis and human immunodeficiency virus infections among inner city parturient women

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To study the relationship of cocaine use to syphilis and human immunodeficiency virus infections a blinded urine and serum survey was performed among parturient women at an inner city hospital. Discarded urine samples of 1206 parturient women were saved and given code numbers that were also assigned to data sheets containing nonidentifying information, including prenatal care status and syphilis serologic results. In the latter part of the study blood remaining after syphilis serologic tests were performed (n = 480) were tested for human immunodeficiency virus antibodies. Overall 12.9% of urine samples had cocaine derivatives, 1.4% opiates, 1.5% marijuana, 0.0% benzodiazepine, and 0.3% methadone. The prevalence of positive rapid plasma reagin tests was 18.7% among patients with positive urine toxicologic tests for cocaine and 2.41% for patients wtih negative urine tests (odds ratio = 9.3, 95% confidence interval 5.2 to 16.5, $p < 0.001$). Fluorescent treponemal antibodies were also significantly more frequent among patients with positive urine samples. Four of 53 (7.6%) patients with positive urine toxicologic screens were human immunodeficiency virus antibody positive compared with six of 427 (1.4%) women with negative screens (odds ratio = 5.7, 95% confidence interval = 1.4 to 21.5, $p = 0.019$). Cocaine patients with positive cocaine screens and with syphilis or human immunodeficiency virus had prenatal care in 6 of 21 (28.6%) and 0 of 4 (0%) cases, respectively, while patients with negative cocaine screens and syphilis or human immunodeficiency virus had prenatal care in 13 of 18 (72.2%) and 5 of 6 (83.3%) cases, respectively ($p = 0.010$ and $p = 0.048$). Cocaine use appears to be associated with both the acquisition of human immunodeficiency virus and syphilis and the failure of infected individuals to utilize prenatal services. (Am J Obstet Gynecol 1990;163:521-6.)

Key words: Cocaine, syphilis, human immunodeficiency virus, prenatal care

The National Institute on Drug Abuse has estimated that in 1986 3 million people in the United States abused cocaine regularly.[1] Use by pregnant women, which can have serious consequences for both mother and child, has been reported to be common in inner city communities.[2] As cocaine use has become epidemic among indigent pregnant women, acquired immunodeficiency syndrome and syphilis have been spreading into the same population. The prevalence of human immunodeficiency virus (HIV) infection among pregnant women in New York City is 1.3% with even higher rates reported from the Bronx (1.9%), Newark (4.3%), and Miami (4.2%).[3, 4] Syphilis rates in endemic communities have increased 70% to 130% between 1986 and 1987.[5] The incidence of congenital syphilis has also risen dramatically, particularly in endemic areas such as Florida, Texas, California, and New York City.[6] The population that is disproportionately infected by both HIV and syphilis is urban, poor, minority women.

The occurrence of high rates of cocaine use and high rates of HIV and syphilis in the same areas is undoubtedly more than coincidence. The fact that shared needles can lead to HIV transmission, for example, is well documented. Intravenous use of cocaine has been reported to significantly increase the risk of HIV infection among intravenous drug users,[7] and there is anecdotal evidence that the use of nonparenteral forms of cocaine can contribute to the sexual acquisition of HIV and other sexually transmitted diseases.[8]

To date, published studies of the relationship of cocaine to HIV and syphilis have relied on patient histories elicited from specific populations (e.g., prostitutes) and are therefore limited in characterizing associations beyond the selected group, and none of these studies examined pregnant women.[8, 9] Since HIV and syphilis, as well as cocaine, have potentially serious consequences for the health of women and children in the

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mass 725,000 d) will hinder its access to the extracellular matrix.[19, 20]

The amount of collagenase recovered from first (Triton) extract of the placenta represents two thirds of the total enzyme present. The remaining one third is recovered in the second (heat) extract. These results are similar to those found in human cervix, suggesting a functional similarity in enzyme distribution between the two organs.[10] Collagenase is produced by stromal cells (e.g., fibroblasts, smooth muscle cells) in a latent form (procollagenase) that is inactive and has low affinity for collagen substrate. The same cell that produces procollagenase also coordinately produces stromelysin, which activates procollagenase.[21] Active collagenase has a high affinity for fibrillar collagen and results in cleavage of the triple helix of collagen (for review on collagenase see Stricklin and Hibbs[22]). The presence of excess tissue inhibitor of metalloproteinase in human placenta, which inhibits active collagenase, suggests that collagen turnover in the extracellular matrix is well controlled and possibly highly localized at the microenvironment of active remodeling of collagen. This is in agreement with the finding that mouse trophoblasts in culture digest only the extracellular matrix immediately beneath the cells, with no evidence of digestion of the matrix beyond the periphery of the trophoblast outgrowth.[23] This biologic property of the trophoblast may play a significant role in implantation and attachment of the placenta to the myometrium without damage to remote areas.

This study demonstrates that human placenta at term is rich in collagenase and contains more enzyme than maternal serum. Assuming the wet weight of placenta at term to be 500 gm, it would contain 2480 and 1865 U of active and latent collagenase, respectively. These levels are 1.6- to 3.6-fold higher than those in the total maternal circulation.[9] Therefore it is possible that serum collagenase may originate from the placenta. This possibility is considered highly unlikely for the following reasons: (1) Active collagenase in placenta has a high affinity for fibrillar collagen substrate, which is abundant in the extracellular matrix. Assuming the presence of a loosely bound pool of active collagenase, the presence of excess tissue inhibitor of metalloproteinase makes it unlikely that a free active collagenase will find its way to the circulation. (2) Serum collagenase levels in pregnancy do not significantly differ from those in nonpregnant women. If placenta contributes to serum collagenase, higher levels of serum collagenase are expected in pregnancy than those encountered in nonpregnant state. (3) Serum collagenase levels are higher 1 day post partum in the absence of placenta than those immediately at delivery. (4) The presence of lower umbilical cord blood collagenase levels than those in maternal circulation is in agreement with this conclusion; although by itself it is not conclusive evidence because human chorionic gonadotropin for instance, which is produced by the placenta, crosses mainly to the mother and not to the fetus, resulting in lower umbilical cord blood levels.[24]

We have previously shown that the onset of labor leads to an increase in collagenase in uterine cervix and in the circulation in women at term. In this study a significant increase in total placental collagenase in labor was also shown. Hormonal signals that lead to the onset of labor also lead to an increase in collagenase production. Studies of hormonal regulation of collagenase production by human placenta therefore may be of value in understanding the mechanisms of implantation and parturition.

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inner city, a blinded urine and serum survey was conducted to more fully define the association between cocaine use and HIV and syphilis in pregnancy. An attempt was also made to relate the use of cocaine to the utilization of prenatal care services particularly by women infected with HIV and syphilis.

Material and methods

Patients. Between Oct. 18, 1988 and March 1, 1989, 1439 women giving birth at a municipal hospital in New York City had urine samples, which otherwise would have been discarded, saved and given code numbers as part of a prospective study of illicit drug use and pregnancy outcomes. All urine samples were collected within 18 hours of admission. Selection was based on admission during shifts when a research assistant was available to collect urine specimens. These shifts varied throughout the day and throughout the week. Although the selection of shifts was not strictly random, the random nature of delivery dates should have produced a random sample. A comparison of drug use between women delivered on weekends and on weekdays revealed no differences in frequency of drug use. In the latter part of the study blood specimens were saved after syphilis serologic tests were performed and were given code numbers matched to urine and data sets. These 480 coded blood samples were subsequently tested for HIV antibodies.

Researchers systematically retrieved information from delivery logs and patient records on days subsequent to admission (before testing of urine and blood). If the chart abstractor noted missing data, the clinician was asked to complete the record. Data sheets did not contain identifiers. Data included drug use history, history of prenatal care, syphilis serologic results, and risk factors for HIV. This information was given the same code number as the urine. In some instances patients either left the hospital before data could be collected (e.g., delivery on days before research assistant off days, $n = 199$) or had neither serologic nor HIV results available on their chart ($n = 34$). Data were available on 1206 patients. Urine toxicologic studies were also run on the patients without complete data sheets to assess potential ascertainment bias. The data collected permitted a cross-sectional comparison between drug use and the presence of syphilis and HIV infection. The study set for this report includes the 1206 patients with both urine and data sets. Of these 726 had syphilis serologic results available but not HIV results (as noted, HIV serologic results were only performed in the latter part of the study), 461 had syphilis and HIV serologic results, and 19 had HIV but not syphilis serologic results (syphilis serologic results were collected from patient records, results were missing in 19 cases).

Data analyses. Confidence intervals and mid p values for the odds ratio estimates of HIV and syphilis for an exposure to cocaine, etc., were based on exact methods.[10-12] The p values were two-tailed. In this approach confidence limits are based on hypergeometric probabilities conditional on fixed margins, which correspond to Fisher's exact test of significance, Exact methods are most useful when sample sizes are small or when disease prevalence is relatively infrequent as in the present study. The actual computations were performed with a computer program developed by Foster.[13]

Laboratory

Toxicology. Urine screening for illicit drugs was performed with a homogeneous enzyme-multiplied immunoassay technique (Syva Emit d.a.u.) for cannabinoid, cocaine, and opiate assays[14-21] (details available on request).

Serologic tests for syphilis. Serum specimens were examined in qualitative rapid plasma reagin card tests. Samples found nonreactive with rapid plasma reagin were recorded as negative and not examined further. Reactive specimens underwent quantitative tests and were also tested in the confirmatory fluorescent treponemal antibody–absorption test. Samples that were rapid plasma reagin reactive, fluorescent treponemal antibody–absorption nonreactive were recorded as biologic false-positive results; those reactive in both tests were recorded as positive.

Tests for HIV-1 antibody. Specimens were examined in a standard HIV-1 enzyme-linked immunosorbent assay (ELISA) antibody procedure (Dupont) followed, where indicated, by a Western blot test. Test results were reported as negative (ELISA nonreactive), inconclusive (blot test nonreactive or equivocal), or positive (blot test reactive). A reactive blot included, as a minimum, virus-specific bands at 160/120 or 41 and 31 or 24 kd.

This study was approved by the Institutional Review Board of State University of New York Health Science Center at Brooklyn and the New York City Health and Hospital Corporation.

Results

A description of the population studied is provided in Table I. The frequency of positive results of urine toxicologic screens among the 1206 study patients was 12.9% for cocaine (90.3% of which were positive only for cocaine), 1.4% for opiates, 1.5% for marijuana, 0.0% for benzodiazepine, and 0.33% for methadone. The frequency of positive results of urine cocaine toxicologic screens among patients with urine collected but without data sheets was 12.6%, which did not differ significantly from results of patients with data sheets. The prevalence of positive rapid plasma reagin test results was 18.7% (28 of 150) for patients with positive urine toxicologic screens for cocaine and 2.4% (25 of 1037) for patients with negative urine test results for

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Preeclampsia in diabetic pregnancies

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Diabetic pregnancies complicated by preeclampsia are of concern because of poor perinatal outcome. However, with improved maternal and fetal surveillance the impact of preeclampsia in diabetic pregnancies is declining. This prospective controlled study compared the incidence of preeclampsia and maternal-fetal outcome in 334 diabetic pregnancies and 16,534 nondiabetic pregnancies. The incidence of preeclampsia was 9.9% (33/334) in diabetic pregnancies compared with 4.3% (716/16,534) in nondiabetic controls. The incidence of preeclampsia rose with increasing severity of diabetes by White classification, but was still 8.9% after exclusion of diabetic patients with nephropathy or chronic hypertension. The perinatal mortality rate per 1000 births was 60 for preeclamptic diabetic patients compared with 3.3 for normotensive diabetic patients. Parity, maternal age, and blood glucose control were similar in preeclamptic diabetic patients compared with normotensive diabetic patients. We conclude that preeclampsia is twice as common in diabetic pregnancies compared with normal controls. (Am J Obstet Gynecol 1990;163:505-8.)

Key words: Diabetes mellitus, preeclampsia, pregnancy, White classification

One of the first suggestions that the incidence of preeclampsia was increased in diabetic pregnancies originated from the Joslin Clinic records, which indicated a 50% incidence before 1938.[1] Subsequent reviews from both North American and British centers from 1953 to 1963 showed an average incidence of preeclampsia in diabetic pregnancies of 25%.[2] However, there were marked variations between centers (8% to 48%), which reflected differences in diagnostic criteria and management. In 1965, Pedersen[3] suggested a new classification for prediction of the outcome of pregnancies complicated by diabetes mellitus. This described four signs of poor prognosis in pregnancy (PBSP classification or Prognostically Bad Signs in Pregnancy), one of which was preeclampsia. This system complemented the White classification, which also attempted to predict perinatal outcome on the basis of age of onset, duration of diabetes, and other diabetic complications.[4] Use of the White classification suggested that the incidence of preeclampsia in diabetic pregnancies increased significantly with the severity of diabetes.

Since the introduction of these classifications, the course and outcome of diabetic pregnancies have greatly changed. As a result doubt has been expressed

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cocaine (odds ratio = 9.3, 95% confidence interval = 5.2 to 16.5, $p = <0.001$) (Table II). Information on confirmatory fluorescent treponemal antibody–absorption test was available for 22 of the 28 patients with cocaine-positive results and positive rapid plasma reagin, and 22 of the 25 patients with cocaine-negative results and reactive rapid plasma reagin. Among patients with cocaine-positive results 21 of 22 (95.5%) had confirmation by fluorescent treponemal antibody–absorption test, while 18 of 22 (81.8%) positive rapid plasma reagin tests among patients with cocaine-negative results were confirmed. The odds ratio of a positive rapid plasma reagin test with a confirmatory positive fluorescent treponemal antibody–absorption test among cocaine users was 9.6 (21/144 vs. 18/1034), 95% confidence interval = 5.0 to 18.8, $p < 0.001$. There were no positive rapid plasma reagin tests among those with opiate metabolites in the urine.

HIV and urine results were available from 480 patients. Four of 53 (7.6%) patients with positive urine screens for cocaine were HIV antibody positive compared with 6 of 427 (1.4%) patients whose urine was negative for cocaine (odds ratio = 5.7, 95% confidence interval = 1.4 to 21.5, $p = 0.019$). None of the 10 HIV-positive patients had other drugs documented in the urine. Among the six patients with HIV-positive, cocaine-negative results one acknowledged intravenous drug use and two were from countries where HIV is endemic. Among the four patients with HIV-positive, cocaine-positive results one acknowledged intravenous drug use in the past. (Only 9 of 115 [7.8%] patients whose medical history included cocaine use noted that they took it parenterally, with the rest either smoking it [$n = 66$] or snorting it [$n = 40$]). Among nine of the 10 HIV-positive patients who had rapid plasma reagin tests, one had a positive result. This can be compared with 15 positive rapid plasma reagin tests among 458 HIV-negative patients (odds ratio = 3.7, 95% confidence interval 0.2 to 25.2, $p = 0.306$).

Among the 10 patients with HIV-positive results five had no prenatal care, four had care at the study institution, and one reported care elsewhere, which was undocumented. Among the 470 patients with HIV-negative results prenatal care status was recorded on the charts of 457. Sixty-eight (14.9%) had no care, 334 (73%) had care at the study site, and 55 (12.1%) had undocumented care elsewhere. None of the four patients with HIV-positive, cocaine-positive results had prenatal care, compared with five of six patients with HIV-positive, cocaine-negative results who had some care ($p = 0.048$) (Table III). Among patients with positive fluorescent treponemal antibody–absorption tests and known care status ($n = 39$), 20 (51.3%) had no care, 17 (43.6%) had care at the study hospital, and 2 (5.1%) had undocumented care elsewhere. Patients who had positive fluorescent treponemal antibody–absorption tests and cocaine-positive results had some prenatal care in six of 21 (28.6%) cases, while patients with positive fluorescent treponemal antibody–absorption tests and cocaine-negative results had prenatal care in 13 of 18 (72.2%) cases ($p = 0.010$) (Table II). Among patients with positive rapid plasma reagin tests who were not cared for at the study hospital ($n = 29$), 17 (58.6%) had been seen in an emergency room during the prenatal period.

Table I. Description of study population

	No.	*%*
Race		
Black	959	79.5
Hipsanic	178	14.8
White	5	0.4
Oriental	5	0.4
Unknown	59	4.9
Parity		
0	436	36.2
1	355	29.4
2	227	18.8
3	96	8.0
4	51	4.2
5	17	1.4
6	17	1.4
Unknown	7	0.6
Average	1.25(± 1.38)	
Occupation		
Unemployed	618	51.2
Secretary	62	5.1
Nurse	15	1.2
Health aide	65	5.4
Business	48	4.0
Student	24	6.1
Unknown	324	26.9
Place of birth		
Haiti	133	11.0
Other Caribbean	417	34.6
United States	459	38.1
West Africa	25	2.1
Other	13	1.1
Unknown	159	13.2
Medical status		
Hematocrit		
<35%	523	43.4
≥35%	633	56.6
Mean value (%)	32.3(± 11.136)	
Hypertension		
Yes	53	4.4
No	1153	95.6

Comment

We have found among a group of inner city parturient women that detection of cocaine derivatives in urine samples was significantly associated with positive rapid plasma reagin tests, fluorescent treponemal antibody–absorption antibodies, and HIV antibodies in maternal blood. Patients with syphilis or HIV infections, particulary those who used cocaine, often had received no prenatal care.

Table I. Incidence of preeclampsia in diabetic pregnancies grouped by White classification

White Class	Total no.	Preeclampsia	
		No.	%
A_1	114	11	9.6
A_2	103	6	5.8
B	46	5	10.9
C	61	8	13.1
D,F,R	10	3	30.0
TOTAL	334	33	9.9

as to whether the incidence of preeclampsia in diabetic pregnancies is now higher than expected in nondiabetic pregnancies.[1,2] This prospective controlled trial was undertaken to assess whether the incidence of preeclampsia was greater in diabetic pregnancies as compared with nondiabetic controls, and if an increased incidence was shown, whether it was related to glycemic control, age, parity, duration of diabetes, or the presence of diabetic complications.

Material and methods

The patient population for the trial consisted of all pregnant diabetic women who attended the Ottawa Civic Hospital Maternal-Fetal Day Unit from January 1, 1979, to December 31, 1986. The control population comprised pregnant (nondiabetic) women delivered in the same hospital over the same period of time. Diagnosis of preeclampsia was made on the basis of the criteria of the Committee on Terminology of the American College of Obstetricians and Gynecologists (1972).[6] Blood pressure measurements were taken from the upper arm with the patient in the lateral position every 2 weeks from 28 to 36 weeks' gestation and weekly or twice weekly according to maternal and fetal monitoring needs from 36 weeks' gestation to delivery. Serial measurements of serum uric acid, creatinine, and blood urea nitrogen levels were performed every 2 weeks during the third trimester. Diagnosis of gestational diabetes was made on the basis of the National Diabetes Data Group criteria for gestational diabetes.[7]

Management of the diabetic pregnancies followed the guidelines suggested by the American College of Obstetricians and Gynecologists.[8] The principle of perinatal care was outpatient management while awaiting fetal pulmonary maturity. Hospital admissions were limited to obstetric indications, diabetic complications, and delivery. Evaluation of blood glucose control was accomplished by frequent fasting and postprandial levels measured 1 hour after breakfast, lunch, and dinner. Home glucose monitoring was accomplished by Chemstrip measurements (Bio-Dynamics, Indianapolis) two to four times daily supplemented by laboratory estimations of blood glucose levels. The mean glucose levels were determined on the basis of an average of 50 readings per patient. Goals for blood glucose control were fasting <100 mg/dl (<5.5 mmol/L) and <140 mg/dl (<8.0 mmol/L) postprandially. Patients with gestational diabetes were initially treated by diet alone according to the dietary recommendations of the American Diabetes Association.[9] Insulin supplementation was added if target blood glucose levels were not reached after 2 weeks of dietary control. Type I insulin-dependent diabetic patients were controlled with neutral protamine Hagedorn and regular insulin injection administered two or three times a day in addition to diet. Antepartum fetal monitoring consisted of nonstress testing weekly or more frequently if indicated from 34 weeks' gestation to delivery in the case of type I diabetes. After a nonreactive nonstress test further evaluation of fetal status was made by a biophysical profile. Fetal growth was assessed by serial ultrasonography every 2 to 3 weeks in the third trimester. Pregnancies were delivered at term unless complicated by obstetric or other medical factors.

Women were grouped according to White classification only for the purpose of statistical analysis.[4] For such analysis, White Class A was subdivided into A_1 (gestation diabetes, diet controlled) and A_2 (gestational diabetes, diet and insulin controlled). Class D (four) and Classes F and R (six) were grouped together to facilitate analysis. Statistical analysis was performed by the unpaired Student t test or χ^2 test where applicable.

Results

A total of 334 diabetic pregnancies were studied over the period 1979 to 1986 inclusive. When grouped according to White classification the distribution was Class A_1, 114; A_2, 103; B, 46; C, 61; D, F, and R, 10. The control population comprised 16,534 nondiabetic women delivered in the same obstetric unit over the same period of time. The incidence of preeclampsia in diabetic pregnancies was 9.9% (33/334) compared with 4.3% (716/16,534) in nondiabetic controls. The incidence of preeclampsia rose with increasing severity of diabetes according to White classification (Table I). After exclusion of diabetic patients with nephropathy or chronic hypertension the incidence was 8.9%.

The perinatal mortality rate for preeclamptic diabetic patients was 60 per 1000 live births (2/33) compared with 3.3 per 1000 live births (1/301) for normotensive diabetic patients. The perinatal mortality rate for all diabetic pregnancies was 9 per 1000 live births. Perinatal loss occurred at 25 and 27 weeks' gestation because of intrauterine death in two preeclamptic Class F diabetic patients after sudden exacerbation of hypertension and at 31 weeks' gestation because of prematurity after premature labor in a normotensive Class B diabetic patient.

There was no statistically significant difference in ma-

Table II. Association of cocaine use with HIV, reactive plasma reagin, and fluorescent treponemal antibody—absorption status

	Cocaine-positive		*Cocaine-negative*		*Odds ratio*	*95% Confidence interval*	*p Value*
	n	%	*n*	%			
HIV	4/53	7.55	6/427	1.41	5.7	1.4-21.5	0.019
Fluorescent treponemal antibody–absorption	21/144*	14.58	18/1034*	1.74	9.6	5.0-18.8	<0.001

*Excludes patients with positive reactive plasma reagin and unknown fluorescent treponemal antibody—absorbtion test result.

Table III. Prenatal care status of patients with HIV and syphilis

	Cocaine-positive			*Cocaine-negative*			
	No care	*Hospital*	*Other**	*No care*	*Hospital*	*Other**	*p Value†*
HIV-positive	4	0	0	1	4	1	0.048
Fluorescent treponemal antibody–absorption positive	15	6	0	5	11	2	0.010

*Patients claim to have seen someone for care during the pregnancy though no records were available to physicians at the delivery site.

†Care of any kind (hospital or other) among women with cocaine-positive versus cocaine-negative results.

The use of cocaine by women is epidemic in many areas of the United States.[22] HIV and syphilis infections have been increasing in the same populations (poor, minority) in which cocaine has become a major drug of abuse.[4, 5, 23-27] Recent data on HIV incidence among army personnel, for example, found rates to be higher among black women than among white men.[23] Syphilis rates also have risen dramatically in many areas of the country. The incidence of primary and secondary syphilis among women in New York City rose from 541 cases in 1986 to 1841 by 1988. Congenital syphilis has shown a parallel rise, going from 60 to 357 cases in the same period.[28]

A higher prevelance of syphilis or HIV infection has significant implications for programs designed to address these problems in pregnancy. The Centers for Disease Control and the American College of Obstetricians and Gynecologists have promulgated guidelines for active intervention, within the context of prenatal care, for both illnesses.[29, 30] For HIV those programs focus on counseling, testing, and informed reproductive choice while for syphilis the focus is on routine testing and treatment. Cocaine has the potential to decrease the utility of these programs while increasing the need for them. In regard to pediatric HIV disease, for example, researchers have shown that "early identification of HIV infection . . . combined with appropriate counselling may decrease the number of children born with perinatal HIV infection, by allowing women to elect early termination of pregnancy."[31] Cocaine use, however, may nullify any potential public health benefits from prenatal counseling programs. The implications for pediatric HIV disease will become even more significant if, and when, antepartum therapy to reduce perinatal transmission becomes available.

We also found that many patients with positive rapid plasma reagin tests who did not have prenatal care had other contact with the health care system (emergency services). Cocaine use may increase the need to consider more aggressive surveillance and intervention for perinatal diseases in less traditional settings (e.g., syphilis screening in emergency rooms with community outreach to women who have positive tests, HIV counseling, and drug counselling on postpartum wards).

As noted, cocaine not only reduces the likelihood of treatment but also has been associated with increased acquisition of disease. The association of these diseases with drug use can partially be explained by the sharing of needles, which can act as vehicles of disease spread. Indeed 2 of 20 HIV-positive women in our study had past intravenous drug use documented in their records, and other HIV-positive patients also may have used intravenous drugs in the past but chose not to report it to health care personnel. Chaisson et al.[7] reported that the intravenous use of cocaine is associated with an increased risk of HIV infection among intravenous drug users. Although parenteral transmission of syphilis has not been as carefully documented as has been HIV transmission, spread from inadvertent inoculation has been reported.[32]

It has also been suggested that sexual risk taking contributes to the increased prevalence of HIV among women who use cocaine.[8, 9] Evidence for that phenomenon has come in large part from interviews with prostitutes, which suggest that exchange of sex for drugs

ternal age between preeclamptic and normotensive diabetic patients (preeclamptic diabetic patients, 27.9 years ± 5.6 SD; normotensive diabetic patients, 28.9 years ± 4.8 SD). The ratio of multigravid to primigravid patients was also similar in both groups (preeclamptic diabetic patients, 1:2.27 or 11/25; normotensive diabetic patients, 1:2.13 or 95/203). Delivery before 36 weeks' gestation was four times more likely when preeclampsia complicated a diabetic pregnancy (preeclamptic diabetic patients, 27.8%; normotensive diabetic patients, 7.8%). Mean birth weights were not significantly lower in preeclamptic diabetic patients compared with normotensive diabetic patients of the same gestational age when born after 35 weeks' gestation. Before 35 weeks' gestation birth weights were significantly lower in the preeclamptic patients with diabetes (Table II).

Mean fasting venous plasma glucose levels (preeclamptic diabetic patients, 88.2 mg/dl ± 21.6 SD; normotensive diabetic patients, 82.8 mg/dl ± 16.2 SD) and mean 1 hour postprandial venous plasma glucose levels (preeclamptic diabetic patients, 127.8 mg/dl ± 27.0 SD; normotensive diabetic patients, 126.0 mg/dl ± 23.4 SD) were not significantly different. Mean third trimester serum uric acid levels were significantly higher in preeclamptic diabetic patients (preeclamptic diabetic patients, 4.6 mg/dl ± 1.1. SD; normotensive diabetic patients, 4.1 mg/dl ± 0.9 SD; $p < 0.05$). Mean third trimester serum creatinine (preeclamptic diabetic patients, 0.67 mg/dl ± 0.13 SD; normotensive diabetic patients, 0.6 mg/dl ± 0.1 SD) and mean third trimester blood urea nitrogen levels (preeclamptic diabetic patients, 10.2 mg/dl ± 2.2 SD; normotensive diabetic patients, 9.1 mg/dl ± 2.2.) were not significantly different.

The incidence of chronic hypertension in all diabetic pregnancies was 3.89% (13/334) compared with 1.6% (265/16,534) in the nondiabetic population.

Table II. Comparison of mean birth weight of infants of preeclamptic diabetic and normotensive diabetic patients according to gestational age

Gestational age (wk)	*Mean weight (kg ± SD)*		*p Value*
	Preeclamptic diabetic infant	*Normotensive diabetic infant*	
38-41	3.46 ± 0.63	3.48 ± 0.51	NS
35-37	3.17 ± 0.65	3.29 ± 0.64	NS
32-34	1.61 ± 0.31	2.58 ± 0.49	<0.001

Comment

Diabetic pregnancies complicated by preeclampsia are of concern because of the increased perinatal morbidity and mortality seen in this situation.[1] Many of the early reports of diabetes in pregnancy commented on the high incidence of preeclampsia and the associated fetal loss.[2] Bachman[11] recorded a 21.7% incidence of preeclampsia in 1450 viable pregnancies reported by American and British clinics between 1947 and 1951. A later review by Kyle[2] of preeclampsia in diabetic pregnancies in 10 series from 1953 to 1960 suggested an average incidence of 25%.

With improved maternal-fetal management and surveillance there has been a suggestion that the incidence of preeclampsia in diabetic pregnancies is declining.[12] Kitzmiller[12] noted an incidence of only 5% preeclampsia in 147 type I diabetic patients, and suggested that modified bed rest at home was in part responsible for the decline.[12] However, Kitzmiller excluded Class F diabetic patients from the analysis on the basis that a diagnosis of superimposed preeclampsia in women with diabetic nephropathy was impossible to make with certainty. A review of pregnancy complications among diabetic women (1965 to 1985) found an overall rate of 11.7% in four studies.[5] Two of these studies failed to find an increased incidence of preeclampsia in diabetic pregnancies (Classes A-R,[12] and Class A alone[13]). Two other studies suggested a significantly higher rate of preeclampsia in diabetic patients (Classes B-R[14] and Classes A-R[16]). The present study is the first prospective study of which we are aware that compares preeclampsia in diabetic pregnancies with a nondiabetic group. It confirms the finding of some retrospective studies of diabetic pregnancies that the incidence of preeclampsia increases with the severity of diabetes by White classification.

The reasons suggested for this increased incidence have been numerous. Hagbard[15] concluded that the increased rate of preeclampsia seen in his series was because diabetic patients were more likely to be primigravid women. Our study has failed to confirm this suggestion inasmuch as a similar ratio of primigravid/multigravid women were seen in both preeclamptic and normotensive diabetic pregnancies. Kitzmiller et al.[12] postulated that the high incidence of preeclampsia was related to inclusion of Class F diabetic patients in those studies. The diagnosis of superimposed preeclampsia in Class F diabetic patients is impossible to make with certainty because many diabetic patients with nephropathy are hypertensive and show worsening of proteinuria as the pregnancy progresses. However, our study shows an overall incidence of 8.9% of preeclampsia when Class F diabetic patients and those with chronic hypertension are not included. This is still double the nondiabetic incidence (4.3%), and suggests that other factors must be implicated. Results of renal function testing in the form of third trimester blood urea nitrogen and serum creatinine levels were also similar in both preeclamptic and normotensive pa-

might be linked to outbreak of sexually transmitted diseases.[8, 9] These interview-based studies may be subject to recall bias since the stigma attached to intravenous drug use may be greater than that associated with nonparenteral use. Our findings are consistent with a hypothesis of sexual transmission. None of the HIV-positive patients had opiates in the urine and eight of 10 denied intravenous drug use. Overall, athough misclassification bias must be strongly suspected, only 7.8% of patients who acknowledged cocaine indicated that they injected it.

The mechanisms through which cocaine enhances sexual risk taking still remain to be clarified. Some risk behaviors may have financial incentive. Although an individual "dose" of cocaine ("crack") may be cheap, the effect of the drug is short-lived and multiple dosing occurs throughout the day. The mechanisms available to indigent women to support a cocaine habit are severely limited and a direct barter of sexual favors for cocaine is not an unlikely event.[33] Cocaine also may have physiologic effects relating to sex; it has been reported both to enhance and to inhibit sexual activities.[34]

A potential for several types of bias exists in this study. Misclassification bias exists in this study since cocaine users who have not recently been exposed to cocaine will be classified as nonusers. This bias, however, would work in the direction of the null hypothesis and in fact understate the influence of the drug on disease acquisition. Cocaine users may be less likely than nonusers to seek treatment for syphilis, and therefore cocaine users may be more likely to be untreated and identified in a cross-sectional study such as this one. This bias would tend to overstate the association. These biases would not affect the association of HIV and cocaine use since evidence of infection is not influenced by treatment. Finally cross-sectional studies limit the inferences that can be made regarding the temporal sequence of cause and effect. Prospective designs will be necessary to overcome these limitations.

In sum, the epidemic of HIV infection and syphilis among pregnant women in this community has been confirmed and an association with cocaine has been found. Cocaine also has been linked to reduced utilization of prenatal care services by infected individuals. The importance of HIV infections, syphilis infections, and cocaine use to the reproductive health of minority women in these communities makes it vital that these associations be verified and the contribution of risk sexual behaviors be clarified. In the interim prevention efforts should begin to focus on the treatment of cocaine use since it may be contributing substantively to the spread of syphilis and HIV and to the failure of patients to receive counseling and treatment. Innovative efforts also are needed to reach "unregistered" pregnant women with HIV counseling and syphilis treatment programs.

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tients with diabetes, suggesting that underlying renal disease may not be the factor. However, more sophisticated testing for early diabetic renal involvement through microalbuminuria testing may be required to confirm this finding.

The diabetic control in both preeclamptic and normotensive diabetic groups was similar, as is evident from comparable mean plasma glucose levels before meals and 1-hour after meals during the third trimester. Thus ensuring euglycemia in diabetic pregnancies does not appear to afford protection from preeclampsia.

Earlier surveys of preeclampsia in diabetic pregnancies had suggested that an important factor might be that persons with diabetes were likely to be older because medical advice tended to delay or advise against pregnancy.[2] Our study fails to support this theory inasmuch as maternal age at delivery is the same in preeclamptic and normotensive diabetic pregnancies.

The complication of a diabetic pregnancy by preeclampsia greatly increases fetal morbidity and mortality, as reflected in this series by a significant increase in pernatal mortality (60:1000 preeclamptic diabetic patients compared with 3.3:1000 normotensive diabetic patients) and a significant decrease in birth weight before 36 weeks' gestation. Until the cause of preeclampsia is further elucidated, the nature of this deleterious effect on diabetic pregnancies remains hypothetical. Preeclampsia is characterized by changes in the production rates of several arachidonic acid metabolites.[17] The vasodilating and platelet-aggregation inhibiting prostaglandins (PGI_2 and PGE) are increased in normal pregnancy, but in contrast a relative increase in vasoconstricting, platelet-aggregating prostaglandins (thromboxane A_2 and PGF_2) is seen in preeclampsia. Thus a change in the balance between these two groups of prostaglandins may play an important role in the pathogenesis of preeclampsia. Similar alterations in the metabolism of arachidonic acid to PGI_2 and thromboxane A_2 are seen in diabetes mellitus.[18] Vascular prostacyclin (PGI_2) synthesis is decreased in both patients and experimental animals with diabetes mellitus, and platelet synthesis of thromboxane A_2 is increased. Prostacyclin synthesis is severely depressed in the umbilical arteries of neonates of mothers with both gestational diabetes and type I diabetes mellitus.[19] The increased ratio of thromboxane A_2 to prostacyclin favors increased platelet aggregation and vasoconstriction, which could play a role in predisposition toward preeclampsia in the pregnant patient with diabetes. The altered thromboxane/prostacyclin ratio can be reversed in both diabetic subjects and in preeclampsia by low-dose aspirin therapy.[20] This suggests the possibility of future prophylactic therapy by cyclooxygenase inhibitors for prevention of preeclampsia in the pregnant diabetic patient.

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Rupture of unscarred uterus in primigravid woman in association with cocaine abuse

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Cocaine use in pregnancy has been associated with preterm labor and abruptio placentae. We report a case of rupture of an unscarred uterus necessitating hysterectomy in a patient after cocaine abuse. (Am J Obstet Gynecol 1990;163:526-7.)

Key words: Ruptured uterus, cocaine abuse

As the increase of cocaine abuse in the United States has occurred, so has the use of cocaine in the pregnant population. The association of cocaine abuse with preterm labor, abruptio placentae, and placenta previa has been previously described.[1] We report a case of a primigravid woman with rupture of an unscarred uterus, who presented with abdominal pain after recent cocaine abuse.

Case report

A 19-year-old, nulliparous, black woman was first seen at 32 weeks' gestation complaining of a 2-day history of progressive, unremitting abdominal pain. She denied vaginal bleeding, rupture of membranes, or change in fetal activity. Her pregnancy was complicated by lack of prenatal care and daily intravenous cocaine use. Her last admitted use of cocaine was 2 days before admission, which coincided with the onset of abdominal pain.

Medical history was unremarkable for previous pregnancies or uterine instrumentation. Vital signs were stable. The physical examination was remarkable for extensive needle tracks and edema of the upper extremities. Abdominal examination revealed a fundal height of 30 cm; the uterus was firm and tender to palpation. Vaginal examination revealed no evidence of bleeding or ruptured membranes and the cervix was closed and soft.

The fetal heart tracing was reactive without decelerations and with a rate of 140 to 150 beats/min. The laboratory findings were hematocrit 31%, coagulation profile normal, and urine negative for protein. Sonographic examination was remarkable for a complete placenta previa, possible abruptio placentae, and decreased amniotic fluid. Estimated fetal weight was 1417 gm (<10th percentile for 32 weeks' gestation), suggesting intrauterine growth retardation.

An urgent exploratory laparotomy was performed for management of an acute abdomen with possible abruptio placentae. On opening the abdomen, the fetus was noted in the right upper quadrant of the peritoneal cavity and the uterus was ruptured. A viable female fetus weighing 1510 gm was delivered with Apgar scores of 5 and 7 at 1 and 5 minutes, respectively. Umbilical cord gas values were as follows: arterial pH 7.25, P_{O_2} 41 mm Hg, and P_{CO_2} 52 mm Hg; venous pH 7.27, P_{O_2} 42 mm Hg, and P_{CO_2} 49 mm Hg.

The uterine rupture was anterior and longitudinal; it extended from the fundus to the lower segment.

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Evaluation of the placental site revealed the presence of a retroplacental clot and an adherent placenta. Because of the irreparable damage to the uterus, a hysterectomy, a bilateral salpingectomy, and a right oophorectomy were performed. The patient required one unit of packed red blood cells intraoperatively. Urine toxicology screen was positive for cocaine. The patient's postoperative course was unremarkable. Results of the infant's examination at birth were consistent with intrauterine growth retardation.

Placenta percreta and abruptio placentae were confirmed on pathologic evaluation, as were left hydrosalpinx and chronic right salpingitis.

Comment

Rupture of the unscarred uterus has been associated with grand multiparity, cephalopelvic disproportion, and oxytocin and has rarely been reported in the primigravid woman.[2] Other causes include previous uterine surgery, uterine abnormalities, cornual pregnancy, hydatidiform mole or chorioadenoma destruens, abruptio placentae, and placenta percreta.[2] In this case the contributing factors were placenta percreta and abruptio placentae. The association of cocaine abuse with rupture of the uterus has not, to our knowledge, been reported previously.

Abdominal pain, uterine tenderness, loss of fetal heart tones, hemorrhage, and shock are the most common symptoms of uterine rupture. Abruptio placentae also may present with these symptoms and ultrasound may help differentiate these two conditions. Patients presenting with the above symptoms should be questioned for drug use, and drug screening may be beneficial in those populations known to be at risk. Prompt abdominal exploration may be necessary and was associated with the survival of the infant in our case. Hysterectomy was required in this patient, but suture of the uterus with a less extensive defect may be possible. Cocaine is thought to cause placental vasoconstriction, decreasing blood flow to the fetus. In addition, increased norepinephrine levels may cause an increase in uterine contractility.[1] The hypertension and vasoconstriction associated with cocaine use might have been responsible for the abruptio placentae. A weakened uterine wall from placental percreta may have predisposed our patient to uterine rupture when tetanic contractions occurred as a secondary result of cocaine use. Obstetricians must be aware of these additional potential complications from cocaine abuse in their patients.

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Prognosis for twins with birth weight <1500 gm: The impact of cesarean section in relation to fetal presentation

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The purpose of this study of twins weighing <1500 gm was to evaluate the impact of cesarean section on intrapartum and neonatal mortality, as well as on cerebral palsy and mental retardation. National data held at the Medical Birth Registry was used for identification of cases. The original medical records were retrieved for 862 such twins born between 1973 and 1983. Twins with cerebral palsy and/or mental retardation born between 1973 and 1980 were identified by questionnaires to all rehabilitation centers for disabled children, offices for the Provision of Care for the Mentally Retarded, and to all local Boards of Education throughout Sweden. The analyses, including calculation of relative risk and 95% confidence interval, were performed after stratification for birth weight (250 gm classes) and period of delivery (1973 to 1976, 1977 to 1980, 1981 to 1983). The cesarean section rate increased from 7.7% (1973 to 1976), and 40.5% (1977 to 1980) to 68.9% (1981 to 1983). Concomitantly, intrapartum and neonatal mortality decreased markedly (51.7% to 29.1%) particularly for twin II but to a much lesser extent for twin I. The relative risk for intrapartum and neonatal mortality (vaginal/abdominal birth) did not increase significantly for twin I in vertex presentation (relative risk 2.0, 95% confidence limits 0.9 to 4.3), for twin I in breech presentation (relative risk 1.8, 95% confidence limits 0.7 to 4.3), for twin II in vertex presentation (relative risk 0.6, 95% confidence limits 0.2 to 1.6), or for twin II in breech presentation (relative risk 1.5, 95% confidence limits 0.7 to 3.0). The rate of cerebral palsy and/or mental retardation was 8.8% during 1973 to 1976 and 8.0 during 1977 to 1980 ($\chi^2 = 0.1$, $p > 0.05$). For twins born in breech presentation the handicap rate in the first period (cesarean section rate 6.0%) was the same as in the second period (cesarean section rate 59.6%). The analysis failed to reveal any significant impact of abdominal birth on the fetal outcome for low-birth-weight twins, even when fetal presentation was taken into consideration.
(Am J Obstet Gynecol 1990;163:528-33.)

Key words: Cerebral palsy, cesarean section, neonatal mortality, mental retardation, twins

During labor low-birth-weight twins have an increased risk for malpresentation, cord accidents, and placental separation.[1,2] To avoid these hazards, abdominal delivery has been proposed for pregnancies involving twins with an estimated birth weight <1500 gm.[3] Others have suggested that an attempted vaginal delivery is appropriate for twins in vertex-vertex presentation[4,5]; thus women with the first or the second twin in breech presentation are to be delivered abdominally.

However, most studies have been based on small numbers of cases and these have not been geographically defined populations, which makes interpretation of the results difficult.[6,7] Therefore recommendations for mode of delivery, particularly for twins in breech presentation, have been based on results from studies on singletons.[1,2]

The purpose of this study was to evaluate the impact of cesarean section on intrapartum and neonatal mortality and on long-term morbidity in a relatively large population. Data from nearly all twins weighing <1500 gm, born in Sweden during an 11-year period were used.

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Material and methods

Between 1973 and 1983, 539 twin pairs with at least one twin weighing <1500 gm at birth were identified in a scrutiny of national data at the Medical Birth Registry, Stockholm. Two hundred sixteen of the cotwins weighed ≥1500 gm; these were not included in the analysis; thus 862 twins for the final analysis. Included in the Medical Birth Registry are twin pregnancies reaching ≥28 weeks or <28 weeks if at least one twin was alive at birth. Compared with the official statistics[8] 2.4% of all women with a twin pregnancy delivered in Sweden during the study period were missing from the Medical Birth Registry.

Twenty-eight twins with lethal malformations and 53 pregnancies with antenatal fetal death were excluded from the analyses. To evaluate the effects of factors other than mode of delivery on intrapartum and neonatal mortality (twins who died during or up to 28 days

Table I. Intrapartum and neonatal mortality for twins weighing <1500 gm and the cesarean section rate

	1973-1976 (n = 379)		*1977-1980 (n = 294)*		*1981-1983 (n = 189)*		*Total (n = 862)*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Intrapartum and neonatal mortality	196	51.7	119	40.5	55	29.1	370	42.9
Vaginal birth								
Twin I	78	45.6	35	40.7	13	41.9	126	43.8
Twin II	106	59.2	40	44.9	8	28.6	154	52.0
Abdominal birth								
Twin I	5	31.3	18	32.7	14	22.2	37	27.6
Twin II	7	53.8	26	40.6	20	29.9	53	36.8
Cesarean section rate		7.7		40.5		68.9		32.3

after delivery) the original medical records of all twins were retrieved. The presentation of the fetus was not recorded in 25 cases (3.0%) in the collected material.

In 4.6% (40 twins in 25 pregnancies from 23 different hospitals) the medical records were not found. The missing twins had a similar birth weight distribution compared with the collected material. Intrapartum and neonatal mortality was 47.5% (19/40), not significantly different from that in the study population ($\chi^2 = 0.3$, $p > 0.05$).

Each newborn in Sweden is given a unique personal identification number. Given the identification number, the Central Bureau of Statistics offers access to a population-based registry with up-to-date information (not older than 14 days) on domicile. This made it possible to identify twins with cerebral palsy and/or mental retardation ≥8 years after birth. A total of 357 twins born between 1973 and 1980 were followed up to school age. A questionnaire was sent to the rehabilitation centers ($n = 30$) for disabled children, as well as to the offices for Provision and Care for the Mentally Retarded ($n = 24$) throughout Sweden. A similar questionnaire was distributed to each local Board of Education ($n = 284$) asking for information on school attendance. As a rule, any child with an IQ score below 70 is placed in a special school. All rehabilitation centers, and all local Boards of Education responded to the questionnaire, whereas three of 24 offices for the mentally retarded did not. Twins with Down syndrome were excluded from the analysis.

The Mantel-Haenszel method was used in the statistical analysis.[9] Stratification was made for period of birth (1973 to 1976, 1977 to 1980, 1981 to 1983) and for birth weight (500 to 749 gm, 750 to 999 gm, 1000 to 1249 gm, and 1250 to 1499 gm). The relative risk for intrapartum and neonatal mortality (vaginal/abdominal birth) was calculated with 95% confidence limits.[10] The χ^2 test with 1 degree of freedom was used to analyze differences between groups. A p value <0.05 was considered significant.

Results

The cesarean section rate increased from 7.7% in the first study period (1973 to 1976) to 68.9% in the last period (1981 to 1983), whereas intrapartum and neonatal mortality decreased from 51.7% to 29.1% (Table I). Intrapartum and neonatal mortality for twin II decreased from the first to the last study period, and in a similar manner for twins born delivered vaginally and abdominally, whereas intrapartum and neonatal mortality for twin I remained virtually constant. Twin II had a significantly higher overall intrapartum and neonatal mortality than twin I (47.0% versus 38.6%; $\chi^2 = 6.2$, $p < 0.05$), although this difference was balanced in the last study period.

In the total material the relative risk for intrapartum and neonatal mortality (vaginal/abdominal birth) was 1.5 and the 95% confidence limits 1.0 to 2.3 (Table II). No significant difference was found in intrapartum and neonatal mortality for twin I or twin II in vertex or breech presentation. For twin I in breech presentation an insufficient number of twins rendered statistical testing invalid; the analysis was therefore performed without stratification for period of delivery.

A separate analysis was made for twins born vaginally compared with those delivered by cesarean section when the only indication for the operation was prematurity. In this way the influence of mode of delivery on intrapartum and neonatal mortality could be studied in the most detailed possible way. No significant differences in intrapartum and neonatal mortality in the vaginal and cesarean delivery groups could be found (Table III).

The autopsy rate for dead twins was 83%. The primary cause of neonatal death was immaturity. Other causes were infection and difficult or traumatic delivery.

Table II. Relative risk for intrapartum and neonatal mortality for twins weighing <1500 gm

	Vaginal birth			*Cesarean birth*				
		Intrapartum and neonatal mortality			*Intrapartum and neonatal mortality*			
	Total No.	*No.*	*%*	*Total No.*	*No.*	*%*	*Relative risk*	*95% Confidence interval*
Both twins	584	280	47.9	278	90	32.4	1.5	1.0-2.3
Vertex twin I	221	92	41.6	79	15	19.0	2.0	0.9-4.3
Vertex twin II	141	63	44.7	54	19	35.2	0.6	0.2-1.6
Breech twin I*	66	34	51.5	49	19	38.8	1.8	0.7-4.3
Breech twin II	154	90	58.4	73	26	35.6	1.5	0.7-3.0
Unknown presentation	2	1	50.0	23	11	47.8		

Statistical analysis after stratification for birth weight (250 gm classes) and period of delivery (three classes). Relative risk (vaginal/abdominal birth) with 95% confidence interval.

*Because of insufficient number of twins, statistical testing was performed without stratification for period of delivery.

Table III. Relative risk for intrapartum and neonatal mortality for twins weighing <1500 gm when the indication for cesarean section was prematurity

	Vaginal birth			*Cesarean birth*				
		Intrapartum and neonatal mortality			*Intrapartum and neonatal mortality*			
	Total No.	*No.*	*%*	*Total No.*	*No.*	*%*	*Relative risk*	*95% Confidence interval*
Both twins	584	280	47.9	156	47	30.1	1.4	0.9-2.3
Twin I (as vertex or breech)	287	126	43.6	80	19	23.8	1.9	0.9-4.2
Twin II (as vertex or breech)	295	153	51.9	67	24	35.8	1.1	0.6-2.1
Vertex (as twin I and/or twin II)	362	155	42.8	65	10	15.4	2.2	0.9-5.2
Breech (as twin I and/or twin II)	220	124	56.4	82	33	40.2	1.4	0.7-2.8
Unknown presentation	2	1	50.0	9	4	44.4		

Statistical analysis after stratification for birth weight (250 gm classes) and period of delivery (three classes). Relative risk (vaginal/abdominal birth) with 95% confidence interval.

The rate of twins with cerebral palsy, mental retardation, or both at follow-up 8 years or more after birth is shown in Table IV. One twin died after the neonatal period but before follow-up, leaving 357 infants in the final analysis group. The handicap rate did not change from the first to the second period (8.8% versus 8.0%, respectively). A similar rate was found for handicapped twins ($\chi^2 = 0.5$; $p > 0.05$) born in breech presentation during the first period (cesarean section rate 6.0%) and in the second period (cesarean section rate 59.6%). The handicap rates were similar for twin I (9.4%) and twin II (7.2%).

The cumulative birth weight distributions were similar for vaginal and abdominal births (Fig. 1); however, twins born vaginally in the lowest stratum (500 to 749 gm) weighed 50 gm less. In 85% of twin pregnancies delivered by cesarean section, twins were detected more than 1 day before delivery (Fig. 2). For vaginal births the corresponding figure was <50%. Detection of twin II after birth of twin I occurred in about 10% and 40%, respectively, for abdominal versus vaginal birth.

Comment

The Medical Birth Registry has collected antenatal, intrapartum, and neontal data on nearly all births in Sweden since 1973. Use of this population-based data base afforded the opportunity to collect information on a relatively large number of twins with birth weights <1500 gm. Because presentation is not recorded in the data base, the original medical records were retrieved, which further improved the quality of the data. The deliveries in this study occurred during a period just before the introduction of routine ultrasonographic scanning for all pregnant women (for confirmation of gestational age) in Sweden. This explains the use of birth weight rather than gestational age as an index of maturity.

For twin I in vertex presentation, no significant difference in intrapartum and neonatal mortality was found between vaginal and abdominal birth after stratification for birth weight. Further evidence that abdominal birth did not improve the prognosis to any extent is that intrapartum and neonatal mortality for

Table IV. Rate of cerebral palsy and/or mental retardation at follow-up, ≥8 years after delivery, in relation to mode of delivery for twins born 1973 to 1976 and 1977 to 1980

	Cerebral palsy–mental retardation								
	Vaginal birth			*Abdominal birth*			*Total*		
	Total No.	*No.*	*%*	*Total No.*	*No.*	*%*	*Total No.*	*No.*	*%*
First period: 1973-1976									
Vertex presentation	102	9	8.8	9	0	0	111	9	8.1
Breech presentation	63	7	11.1	4	0	0	67	7	10.4
TOTAL*	165	16	9.7	17	0	0	182	16	8.8
Second period: 1977-1980									
Vertex presentation	75	6	8.0	35	4	11.4	110	10	9.1
Breech presentation	24	1	4.2	35	3	8.6	59	4	6.8
TOTAL*	100	7	7.0	75	7	9.3	175	14	8.0

*Including twins without known presentation.

twin I remained virtually constant for vaginal births, as well as for abdominal births during the first two study periods (Table I).

For twin I in breech presentation, stratification for period of delivery was not done because of an insufficient number of cases. Thus vaginal birth during the first period (when the overall intrapartum and neonatal mortality was higher) was compared with abdominal birth during the last period (when the overall intrapartum and neonatal mortality was lower). This limitation in the analysis would tend to increase the relative risk for vaginal birth. However, the relative risk for intrapartum and neonatal mortality remained insignificant, suggesting that cesarean birth is not a significant factor influencing changes in intrapartum and neonatal mortality.

Intrapartum and neonatal mortality for twin II decreased consistently during the study period but the analysis failed to show that twin II born abdominally had a significantly lower intrapartum and neonatal mortality than twins born vaginally. This is in contrast to the results of other studies.[3, 11] For twin II in vertex presentation the relative risk for intrapartum and neonatal mortality was below 1.0.

When the results are evaluated, several possible confounding factors must be considered. In Sweden a pediatrician is always present at a cesarean birth. This was probably not usually the case at vaginal twin births during the study period. It should be noted that the present analysis might include twins born when the obstetrician may have underestimated viability and may have refrained from intervening because of fetal indications, accordingly influencing the results of vaginally born twins negatively. Support for this negative influence comes from the birth weight analysis of the birth weight in the lowest stratum (500 to 749 gm) in which the twins born vaginally weighed 50 gm less than those born abdominally. Admittedly, only 56 twins had a birth weight <750 gm.

The interpretation of the results is complicated by the fact that when cesarean section is performed because of life-threatening conditions for the fetus (e.g., abruptio placentae) the cesarean section would appear to be a risk factor. The estimated relative risk could contain two counteractive components: one a confounding effect of life-threatening conditions, the other a beneficial effect of cesarean section on fetal mortality. To reduce the former effect, a separate analysis was made in which the sole indication for cesarean section was prematurity. Because of the paucity of cases, this analysis was restricted to twin I or twin II (irrespective of presentation) or to vertex or breech presentation (irrespective of order of birth). In none of the four groups tested was intrapartum and neonatal mortality significantly lower for twins born abdominally than for vaginally born twins.

Most previous studies have indicated the importance of an early twin diagnosis to improve prognosis.[5, 7] A remarkable finding was that about half of the twin pregnancies with vaginal delivery were detected less than 1 day before the delivery, whereas the corresponding figure for abdominal births was 10%. This indicates that women with twin pregnancies finally to be delivered abdominally might have benefited during the pregnancy, compared with women who gave birth normally.

The autopsy rate in this study was 83%. I refrained from further analysis of cause of death for several reasons. It is probable that the results of an autopsy performed in 1973 (when few pediatric pathologists were available) are not strictly comparable with one per-

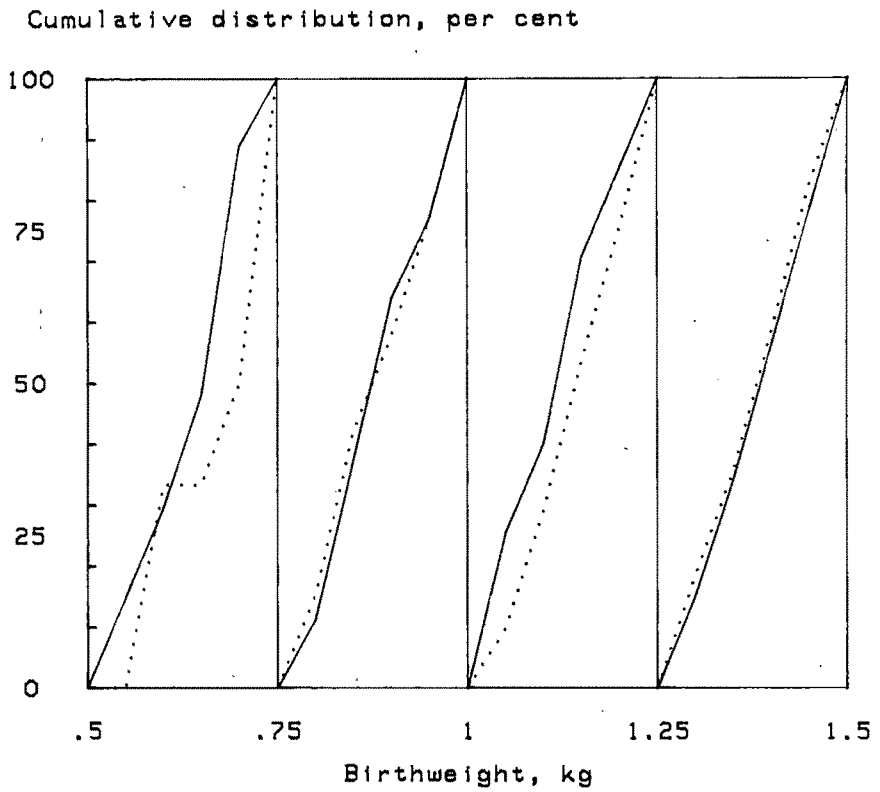


Fig. 1. Cumulative birth weight distribution for twins with vaginal birth *(solid line)* and abdominal birth *(dotted line)*.

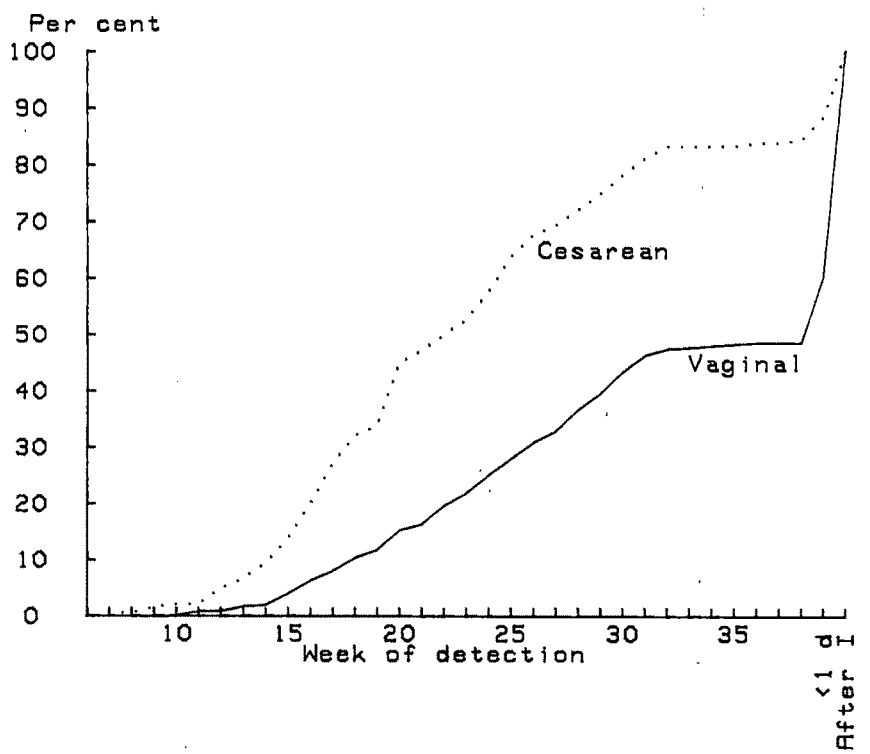


Fig. 2. Week of detection; *<1 d* signifies detection less than 1 day before delivery. A considerable number of twins were not detected until after birth of twin I *(after I)*.

formed in 1983. More significantly, classification by clinical cause is inadequate because several of the definitions are highly subjective.[12] The major impact of the high autopsy rate was that twins with lethal malformations could be excluded from the analysis.

A significant feature of studies of handicapped infants in the Scandinavian countries is the possibility to locate each single infant in a birth cohort, irrespective of the interval between delivery and follow-up. This is made possible by (1) the unique personal identification number given to each newborn (and present in Medical Birth Registry) and (2) information on domicile available from the Central Bureau of Statistics. With information on domicile for each single twin, it is possible to gain reliable data on, for example, school attendance (with one exception, for infants living abroad).

It is noteworthy that in this study 8% to 9% of all twins weighing <1500 gm had cerebral palsy and/or mental retardation at follow-up, 8 years or more after delivery. This proportion did not decrease significantly from the first to the second period (8.8% versus 8.0%). The latter figure (8.0%) could conceivably have been higher because infants with mental retardation are sometimes not identified until or after the beginning of obligatory schooling at 7 years of age.[13] Obviously the rising cesarean section rate seems to have influenced the morbidity rate to a very limited extent. This conclusion includes twins in breech presentation in which the cesarean section rate increased about tenfold from the first to the second period.

A marked overall reduction of the intrapartum and neonatal mortality was seen during the study period, although to a much lesser extent for twin I than for twin II. Concomitantly the cesarean section rate increased from 7.7% to 68.9%. To what degree this increase in abdominal deliveries has contributed to the improved mortality figures cannot be separated from other factors influencing the results. Nevertheless, the cesarean section rate seemed to have little impact on intrapartum and neonatal mortality or cerebral palsy and mental retardation related to twin presentation.

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Recurrent acute fatty liver of pregnancy

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The first reported case of recurrent acute fatty liver of pregnancy confirmed by biopsy is described. In this case a high index of suspicion led to an early diagnosis and intervention with resultant improved maternal and fetal outcome. Electron microscopic examination of a liver biopsy specimen proved more beneficial in confirmation of the diagnosis compared with routine microscopic examination. (AM J OBSTET GYNECOL 1990;163:534-8.)

Key words: Acute fatty liver, electron microscopy, pregnancy

Acute fatty liver of pregnancy is a rare but potentially fatal complication of the third trimester of pregnancy. The exact cause of acute fatty liver of pregnancy is still debatable; however, it has not been described to recur in subsequent pregnancies.[1, 2] We previously reported use of computed tomography in diagnosis of acute fatty liver of pregnancy.[3] The patient described in that report has since returned with a subsequent pregnancy also complicated by acute fatty liver of pregnancy. This article describes the recurrence.

Case report

A 37-year-old black woman, gravida 5, para 3, abortus 1, was seen at 30.5 weeks' gestation with a 2-day history of nausea, vomiting, anorexia, and a low-grade fever. The patient further noted a 1-day history of epigastric pain and decreased fetal movement. Subjectively, the patient offered that the symptoms she was experiencing were identical to those of her previous pregnancy complicated by acute fatty liver of pregnancy and intrauterine fetal demise. Physical examination revealed a blood pressure of 110/80 mm Hg and a pulse of 84 beats/min with no significant orthostatic changes. Temperature was 37.8° C. The abdomen was nontender with fundal height of 22 cm. A single fetus in vertex presentation was noted with a fetal heart rate of 136 beats/min. The cervix was 1 cm dilated but uneffaced. Slight scleral icterus was present, but there was no edema of the extremities. Liver function tests and coagulation profiles had returned to normal 3 weeks post partum after her previous episode of acute fatty liver of pregnancy 16 months earlier. Initial laboratory data included a serum aspartate aminotranferase serum of 790 U/L, serum alanine aminotransferase of 865 U/L, total bilirubin 3.3 mg/dl, γ-glutamyl transpeptidase 342 U/L (normal 5 to 55 U/L), alkaline phosphatase 362 U/L, uric acid 11.4 mg/dl, serum ammonia 28 μmol/L (normal 11 to 35 μmol/L), lactic dehydrogenase 402 U/L, platelet count 307,000/mm³, and plasma glucose 62 mg/dl. The bleeding time was 4 minutes, prothrombin time 13.0 seconds, partial thromboplastin time 33.6 seconds, and hematocrit 39%. A urine dipstick test for protein was negative. A nonstress test was nonreactive with decreased variability and a baseline fetal heart rate of 180 beats/min. The biophysical profile score was 2/10 (2 only for fluid, which was subjectively decreased). The patient had a primary classic cesarean section while under general anesthesia. A 990 gm viable female with Apgar scores of 2 and 5 at 1 and 5 minutes, respectively, was delivered. An arterial cord blood gas sample revealed pH 7.28, P_{CO_2} 51 mm Hg, P_{O_2} 21 mm Hg, with a base excess of −2.8 mmol/L. A Tru-Cut (Travenol Laboratories, Inc., Deerfield, Ill.) needle biopsy of the liver was performed under direct visualization through the same abdominal incision. The patient was transferred to the obstetric intensive care unit for recovery and was monitored there for 3 days. Computerized tomography of the liver was performed on postoperative day 1 and revealed subtle areas of decreased density predominantly in the right lobe of the liver in comparison with the splenic density. These areas of decreased density were consistent with focal fatty infiltration. The patient required intravenous hydralazine on two occasions during postoperative day 1, but none thereafter. Serial laboratory evaluations of plasma glucose remained normal throughout the hospitalization. Elevated aminotransferase and lactic dehydrogenase levels normalized within 7 days of delivery. All hepatitis B titers were negative. Hepatitis A IgG antibody remained positive as detected in the previous pregnancy. The patient was discharged on postoperative day 8. Respiratory insufficiency of prematurity and patent ductus arteriosus developed in the infant, who remained in the neonatal

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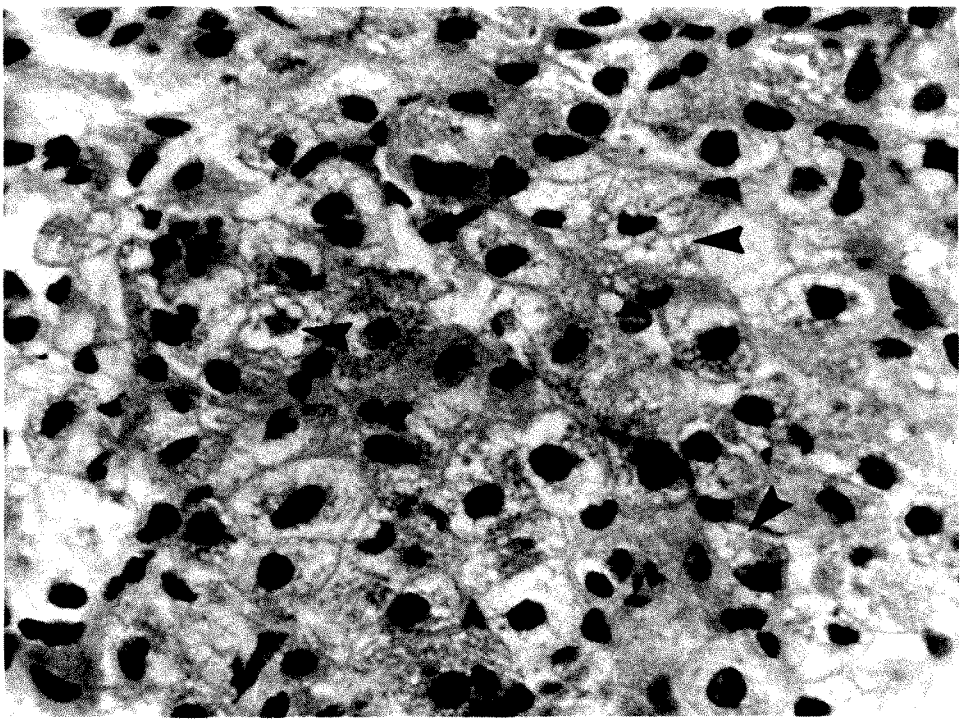


Fig. 1. Liver with small fatty vacuoles *(three arrows)* that do not displace nuclei of hepatocytes. Minimal remnant glycogen storage and no alteration of overall achitecture. (Hematoxylin and eosin. Original magnification ×400, reduced to 73%.)

intensive care unit for 53 days but was discharged at that time in good condition.

Microscopic examination of the liver biopsy was compared with the biopsy from our patient's earlier pregnancy. The current biopsy revealed diffuse low-grade panlobular microvesicular fatty change (steatosis) (Fig. 1) with low-grade portal and parenchymal chronic inflammation, histopathology similar to that previously reported.[3] This fatty change was obvious on hematoxylin and eosin stain; thus oil red O or other special stains were not considered necessary. These lesions were fully consistent with acute fatty liver of pregnancy,[4] but fell short of the histologic changes of severe, often fatal, acute fatty liver of pregnancy.[5, 6] These changes are effectively pathognomonic for acute fatty liver of pregnancy at the light microscopic level.[1-6]

Electron micrographs revealed cellular changes considered to be diagnostic of acute fatty liver of pregnancy. There was maintenance of overall lobular architecture. The vacuolar appearance on hematoxylin and eosin staining was matched by microvesicular fatty deposits with distinctive membrane barriers. There was abundant β-glycogen often bordering the fatty vesicles. Most mitochondria were intact, reflecting the condensed state. The mitochondria in Reye's syndrome have been described as flocculent[7, 8] or with diminished matrix granules,[9] neither of which were detected here. Similarly, lipophagosomes are found frequently in hepatocytes in Reye's syndrome.[7, 8, 10] Only tiny residual bodies were found in the hepatocytes in our patient (Fig. 2). However, rare intramitochondrial crystalline inclusions were noted (Fig. 3), but this has been seen in acute fatty liver of pregnancy[11] as well as in cases of hepatitis B.[12, 13] The nuclei were normal with dispersed grains of glycogen.

Comment

This patient demonstrates that recurrent acute fatty liver of pregnancy can recur. The lack of previous reports of recurrent acute fatty liver of pregnancy may be related to medical counseling against further pregnancies, infrequent use of liver biopsy in such cases, independent patient decisions against further pregnancies, or a low incidence of recurrence.

The case further illustrates that early diagnosis and intervention can result in excellent maternal and fetal outcome in acute fatty liver of pregnancy. The patient was delivered within 60 hours of her initial symptoms and within 3 hours after admission to the hospital. The management of acute fatty liver of pregnancy remains immediate delivery and supportive care.

Although routine microscopic examination was not strictly pathognomonic for acute fatty liver of pregnancy, it was fully consistent. The ultrastructure confirmed the diagnosis. The extent of histologic findings

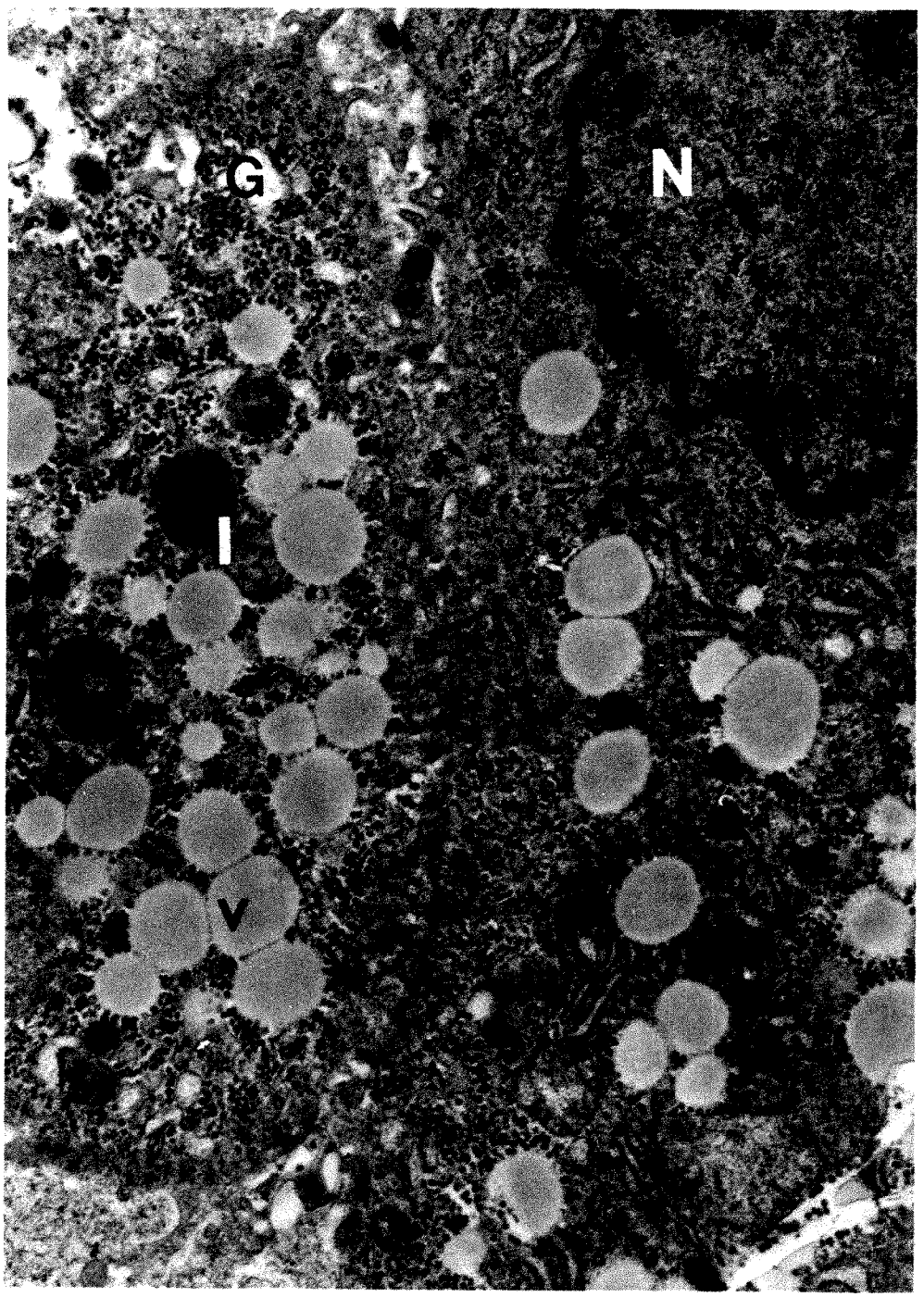


Fig. 2. Transmission electron micrograph of liver biopsy specimen. Microvesicular fatty change *(V)*, abundant β-glycogen *(G)*, and intact, condensed mitochondria *(M)*. Rare mitochondrion with crystalline inclusions *(I)*. Hepatocytic nuclei *(N)* also contain some β-aggregates of glycogen. (Original magnification ×8000.)

can be attributed to early diagnosis and treatment. We suggest routine biopsy for electron microscopy as a means to establish the diagnosis definitively.

Microvesicular cytoplasmic fatty droplets in hepatocytes are also observed in Reye's syndrome.[7-10, 14] Reye's syndrome was unlikely in this patient because of her age, denial of recent aspirin use, no recent clinically apparent viral illnesses, and a total bilirubin consistently >3 mg/dl. Moreover, the ultrastructural distinctions between Reye's syndrome[7-10, 14] and acute fatty liver of

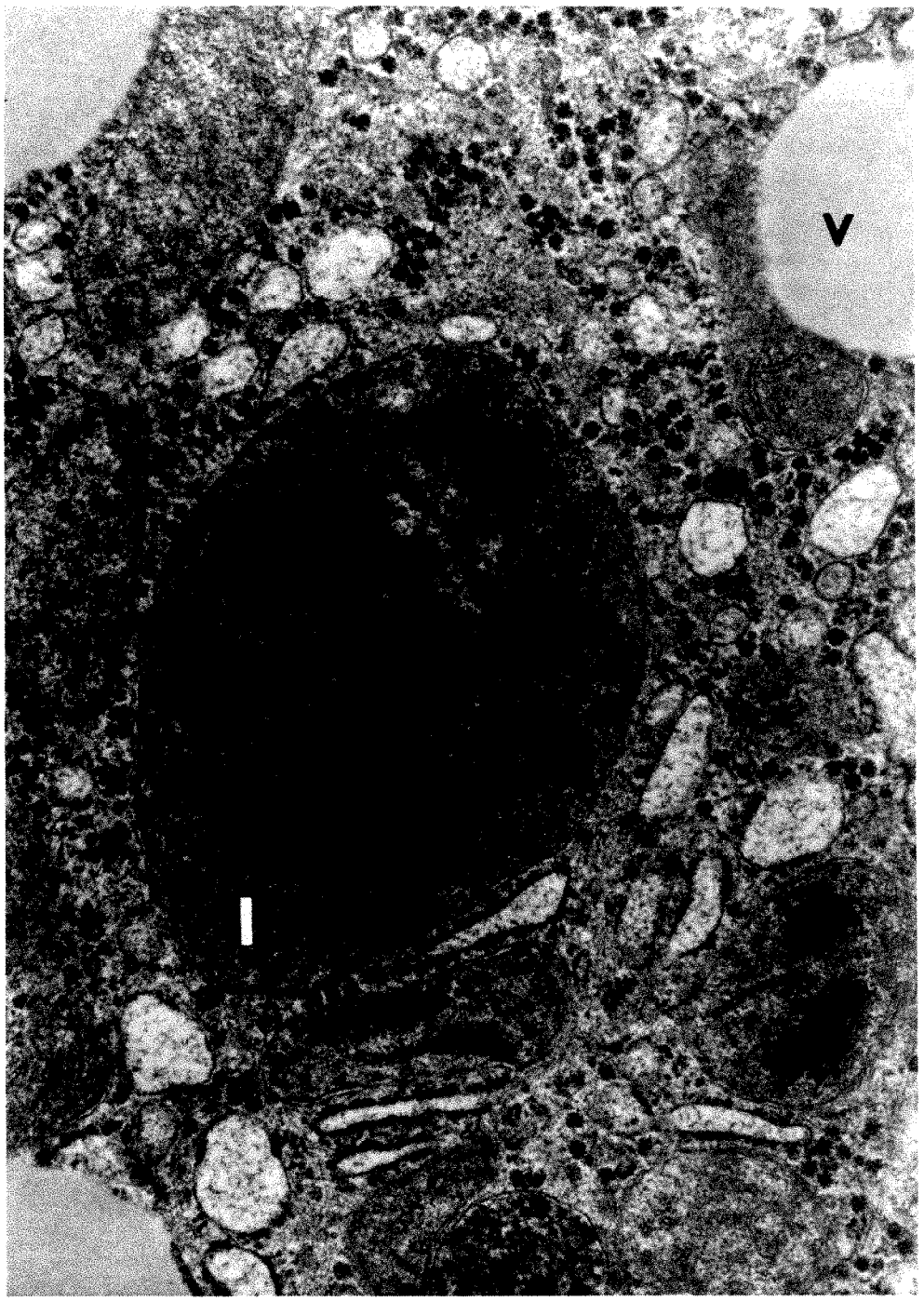


Fig. 3. Transmission electron micrograph of liver biopsy specimen. Microvesicular fatty change *(V)* and enlarged mitochondrion containing numerous crystalline inclusions *(I)*. (Original magnification ×58,700.)

pregnancy[11] indicated that our patient is an example of recurrent acute fatty liver of pregnancy.

Subsequent pregnancies in patients with previous acute fatty liver of pregnancy should be monitored closely for signs and symptoms of acute fatty liver of pregnancy, especially in the third trimester. With a high index of suspicion, an earlier diagnosis of recurrent acute fatty liver of pregnancy can be made, resulting in more rapid intervention and improved maternal and fetal outcome.

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Postpartum coronary artery dissection followed by heart transplantation

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A rare case of coronary artery dissection was observed in a 33-year-old woman on the fourth postpartum day. The ischemic syndrome was followed by aneurysmal dilatation of the left ventricle and progressive heart failure that necessitated cardiac transplantation. The patient is alive and well 3 years after the transplantation. (Am J Obstet Gynecol 1990;163:538-9.)

Key words: Coronary dissection, heart transplantation, postpartum ischemic syndrome

Coronary artery dissection without aortic involvement is a known but rare condition. Less than 60 cases have been reported in the literature. In a recent review Robinowitz et al.[1] reported that 85% of the cases occurred in women, most frequently during the peripartum or postpartum period. Coronary artery dissection in pregnancy or post partum usually appears with sudden collapse and death or with a severe ischemic syndrome. Survival has been reported only occasionally and the diagnosis has been made at autopsy. The left coronary artery is generally involved.

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Case report

A 33-year-old primiparous woman was delivered spontaneously at term on July 23, 1986. Medical history was unremarkable. An electrocardiogram at the thir-

tieth week of pregnancy was normal; 4 weeks later she had a short episode of epigastric pain. On the fourth postpartum day she again experienced severe epigastric pain with posterior irradiation accompanied by profuse perspiration. The electrocardiogram revealed ST segment elevation in leads I and aVL. A gallop rhythm with a protodiastolic third sound was present. An echocardiogram showed hypokinesis of the septum and left ventricular apex. Electrocardiogram evolution indicated an acute transmural anteroseptal myocardial infarction. On day 7 an echocardiogram was consistent with a left ventricular aneurysm and hypokinesis of the apex, distal two thirds of the interventricular septum, and lateral and anterior walls. The serum creatine phosphokinase level was 2120 IU/L, and lactic dehydrogenase was 3239 IU/L. The patient was in a low output syndrome and required intravenous inotropic support. Technetium 99 radionuclide angiography 3 weeks later disclosed left ventricular dilatation with an apical aneurysm and interventricular septal and lateral wall hypokinesis. After referral to Niguarda Hospital the patient underwent heart transplantation in October 1986. She is symptom-free 36 months after operation. She receives low-dose triple-drug therapy (cyclosporine, azathioprine, and prednisone) and leads a normal life.

The heart excised at transplantation weighed 280 gm. Myocardial tissue of the inferior two thirds of the left ventricular anterolateral and anteroseptal walls was replaced by fibrotic scar tissue. The left main and anterior descending branches of the left coronary artery showed a thickened intima but without critical stenosis. There was an organized dissection of the media, with new lumen formation filled by coagulated blood originating 6 mm above the coronary ostium for a length of approximately 18 mm. At histologic examination degenerative changes were present. No periadventitial inflammation was observed. The circumflex branch and the right coronary artery were normal. Pathologic findings were consistent with a large anteroseptal myocardial infarction caused by aneurysmal dissection of the left main and left anterior descending coronary artery, with partially restored vessel patency and organization of the dissected vascular wall.

Comment

Spontaneous primary coronary artery dissection is a rare condition that is most frequently observed in the peripartum period. In almost all cases reported, the medical history was unremarkable and pregnancy and delivery were uncomplicated. It has been suggested that coronary artery dissection may be a result of vasculitis. Localized periadventitial inflammation adjacent to the lesions primarily composed of eosinophilic infiltrate has been reported[2]; however, this might be a secondary reaction rather than a primary lesion. It is more likely that the hemodynamic changes that occur during labor and the straining of delivery may cause intimal disruption or rupture of the vasa vasorum into the medial wall. These mechanisms are probably facilitated by the vascular degenerative changes that occur in pregnancy. A mucoid medial degeneration of the aorta has been found in cases of aortic dissection during pregnancy, and in approximately 40% of cases of coronary artery dissection. None of the reported cases had clinical symptoms of coronary artery dissection immediately after delivery. Ours is only the second case reported in the first week of puerperium, whereas usually coronary artery dissection appears 14 to 90 days post partum. It might be argued that the clotting changes that occur early in puerperium can delay medial bleeding initiated at delivery.

In conclusion, coronary artery dissection is certainly a cause of myocardial infarction during puerperium at least as frequently as thrombosis or embolization. Current therapeutic strategies (fibrinolytic treatment) commonly used in myocardial infarction are entirely inappropriate in these cases. Thus particular caution must be used to distinguish thrombosis from dissection in peripartal myocardial infarction. Early coronary angiography should be performed when necessary to assist in the choice of medical or surgical intervention. To our knowledge this is the first case of postpartum coronary artery dissection successfully treated by heart transplantation.

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Induction of labor with mifepristone (RU 486) in intrauterine fetal death

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In a double-blind controlled multicentric study involving 94 patients with an intrauterine fetal death, we investigated the efficacy and tolerance of mifepristone (RU 486), a steroid compound that antagonizes progesterone action at the receptor level. Success of treatment was defined as the occurrence of fetal expulsion within 72 hours after the first drug intake. Mifepristone treatment (600 mg per day for 2 days) was considered to be effective in 29 of 46 patients (63%). There were only eight successes in 48 patients (17.4%) in the placebo group ($p = 0.001$, χ^2 test). Tolerance was good in the mifepristone group. In the placebo group, disseminated intravascular coagulation occurred in one woman for whom the investigator waited several weeks for spontaneous expulsion. This large double-blind controlled study provides evidence that mifepristone is of interest in the management of intrauterine fetal death. It could provide a pharmacologic alternative to the use of prostaglandins in this indication. (AM J OBSTET GYNECOL 1990;163:540-2.)

Key words: Mifepristone, intrauterine fetal death, induction of labor

Intrauterine fetal death remains a common and serious problem. The risk of complications, such as psychologic distress and disseminated intravascular coagulation, leads most clinicians to induce fetal expulsion when possible. In this respect, prostaglandins provide an effective method of inducing labor and constitute a common approach to the management of intrauterine fetal death. However, their use is limited by contraindications and side effects.

Mifepristone (RU 486, Roussel Uclaf, Paris, France) is a steroid compound that antagonizes progesterone and glucocorticoid actions at the receptor level. It has been successfully used for first-trimester abortion.[1,2] It was also shown to induce labor in an open pilot study of intrauterine fetal death.[3] However, because spontaneous labor can occur during intrauterine fetal death, a placebo controlled study was necessary to confirm this finding.

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Patients and methods

This double-blind study versus placebo was designed to assess the efficacy of mifepristone for labor induction in intrauterine fetal death. The study took place in 10 obstetric and gynecology departments in France and South Africa after approval from an Independent Ethics Committee.

All inpatients who participated in the study gave written informed consent. Inclusion criteria were a gestational age >16 weeks from the last menstrual period and the absence of signs of imminent labor. Women with suspected disseminated intravascular coagulation were excluded from the study. The number of women to be included was calculated to be 100 (50 per group), assuming an expulsion rate of 25% in the placebo group and of 80% in the mifepristone group, for a type 1 and a type 2 error of 0.05.

The patients were randomly allocated to receive treatment with either mifepristone 600 mg (200 mg three times a day) or placebo for 2 days. Treatments were supplied individually packed by Roussel Uclaf after a balanced randomization list was obtained by the method of random permutations. Success was defined by the occurrence of fetal expulsion within 72 hours after the first drug intake. Even in this case, the patients underwent uterine revision. If expulsion had not occurred within 72 hours, intrauterine fetal death was managed according to standard procedure for each center.

Tolerance was evaluated by general and gynecologic examination twice daily and by the following laboratory tests performed before treatment and at expulsion (or at the latest, 72 hours after the first drug intake): hemogram, prothrombin, partial thromboplastin time, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, γ-glucose tolerance, plasma glucose, and creatinine levels. Statistical analysis was performed with the χ^2 test and the Fisher exact test. The p values below 0.05 were considered significant.

Results

A total of 94 women were included in the study (48 in the mifepristone group, 46 in the placebo group). Table I shows that the groups were comparable in terms of age and obstetric parameters. In addition, pretreatment progesterone levels did not differ significantly.

The cause of fetal death was determined in only 30 women: fetal death was attributed to maternal pathology in 15 cases and to fetoplacental abnormality in 15 cases.

For efficacy analysis, two women from the mifepristone group were excluded because they did not meet the inclusion criteria.

Labor occurred within 72 hours after the first drug intake in 29 of 46 patients (63%) in the mifepristone group and in only eight of 46 cases (17.4%) in the placebo group ($p < 0.001$).

Clinical tolerance was good. No significant modifications of blood pressure or heart rate were observed in either group. Intercurrent symptoms were reported with comparable frequency in both groups (Table II).

In the mifepristone group, minimal or moderate uterine bleeding was reported three times but did not require blood transfusion or hemostatic procedure. In the placebo group, disseminated intravascular coagulation occurred in a woman who had not expelled the fetus within 72 hours. Because this woman had a contraindication to the use of prostaglandins, the investigator decided to wait for a spontaneous expulsion. This woman was successfully treated with heparin therapy and underwent uterine revision.

Laboratory data were available for 70 women. The main results are given in Table III. There were no significant variations for any parameters in either treatment group. Furthermore, no abnormal values for hepatic enzymes were found after treatment.

Comment

This large double-blind study confirms that, as shown in a preliminary trial,[3] mifepristone can be useful in the management of intrauterine fetal death. Indeed, mifepristone induced labor in 63% of the patients, as compared with 17.4% in the placebo group.

The success of mifepristone in intrauterine fetal death is lower than that obtained during first-trimester pregnancy interruption.[1, 2] but much higher than that achieved in second-trimester pregnancy interruption when the fetus is still alive.[4] This last point raises the problem of the hormonal control of labor onset in these two situations.

Tolerance was good. Uterine bleeding was reported three times in the mifepristone group. The bleeding, which may have been a result of the antiprogesterone properties of the drug, was moderate and did not require blood transfusion. The only serious adverse event

Table I. Age, obstetric parameters, and pretreatment progesterone levels in the two groups (mean ± SEM)

	Mifepristone (n = 48)	*Placebo (n = 46)*
Age (yr)	27.8 ± 0.8	28.9 ± 0.9
Parity (no. of deliveries)	1.9 ± 0.3	2.1 ± 0.3
Gestational age		
Days of amenorrhea	199.1 ± 7.8	197.5 ± 6.7
Duration of retention* (days)	18.2 ± 4.1	15.1 ± 2.5
Cervical score before treatment†	1.9 ± 0.3	1.7 ± 0.2
Progesterone level before treatment (ng/ml)	61.5 ± 12.1	57.1 ± 7.6

*Interval between fetal death (estimated by ultrasonographic examination and clinical history) and first drug intake.

†Assessed with modified Bishop's score, omitting presentation parameters.

Table II. Side effects reported during trial

	No. of patients	
Side effects	*Mifepristone*	*Placebo*
Headache	0	3
Increase in blood pressure	1	0
Faintness	1	0
Uterine bleeding	3	0
Nausea, vomiting	2	2
Abdominal pain	0	1
Polyuria	1	1
Sweating	1	0
Disseminated intravascular coagulation	0	1

Table III. Laboratory data

	Placebo				*Mifepristone*			
	Pretreatment		*Posttreatment*		*Pretreatment*		*Posttreatment*	
	Mean	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*
Hemoglobin (gm/dl)	12.1	0.2	11.9	0.2	12.2	0.2	12.1	0.2
Hematocrit (%)	35.8	0.7	35.2	0.7	36.5	0.5	36.4	0.6
Platelets (10^3/mm^3)	235.1	10.6	229.5	11.3	243.0	11.4	233.8	12.4
Prothrombin (%)	90.3	2.2	88.2	2.3	92.6	1.7	88.7	2.1
Partial thromboplastin time ratio (%)	9.4	1.1	10.2	1.2	9.8	1.3	8.5	1.2
Glucose (mmol/L)	4.79	0.16	4.69	0.21	4.26	0.10	4.69	0.27
Creatinine (μmol/L)	65.7	2.8	63.8	2.3	58.8	1.5	63.4	2.7

occurred in the placebo group in which a woman suffered from a disseminated intravascular coagulation. It is noteworthy that this woman had a contraindication to the use of prostaglandins and that the investigator waited several weeks for a spontaneous expulsion. This underlies the well-known risk of a prolonged therapeutic abstention.

Biologic tolerance was also satisfactory. There was no significant difference between the placebo and the treatment group. However, this must be considered cautiously because laboratory data were available in only 74% of the cases.

Prostaglandins are commonly used in the treatment of intrauterine fetal death. The success rate with prostaglandins ranges from 91%[5] to 100%.[6] Nevertheless, prostaglandins are not well tolerated and their use is limited by classical contraindications (e.g., hypertension, scarred uterus). Mifepristone could be the treatment of choice in these cases. Moreover, data obtained in first- and second-trimester pregnancy interruption[7,8] indicate that mifepristone enhances uterine sensitivity to prostaglandins, thereby allowing the use of lower doses of the latter to induce abortion. It is likely that this synergistic effect is useful for the management of intrauterine fetal death but it requires further demonstration.

We thank Patricia Sraiki for her assistance.

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Mifepristone (RU 486) failure in an ovarian heterotopic pregnancy

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A patient treated with mifepristone (RU 486), which successfully induced abortion of an intrauterine pregnancy, was discovered to have a heterotopic ovarian pregnancy resistant to this antiprogesterone. The ovarian pregnancy was removed with operative laparoscopy. This case demonstrates for the first time that an ovarian pregnancy may be resistant to treatment with RU 486 at a dose adequate to abort an intrauterine pregnancy. (AM J OBSTET GYNECOL 1990;163:543-4.)

Key words: Mifepristone (RU 486), antiprogesterone, heterotopic ovarian pregnancy, laparoscopy

Although the antiprogesterone mifepristone (RU 486) has been used successfully as an abortifacient in early gestation, it has been reported to fail to eradicate tubal ectopic pregnancy.[1, 2] We report the failure of mifepristone to eradicate an ovarian heterotopic pregnancy in a woman with a coexisting intratuerine and ovarian pregnancy. This ovarian pregnancy was managed successfully by operative laparoscopy.

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Case report

A 27-year-old primigravid woman was seen at the Los Angeles County/University of Southern California Medical Center 39 days after her last menstrual period and requested induced abortion with mifepristone. Initial screening by the institutionally-approved protocol included a normal physical examination, a serum β-subunit human chorionic gonadotropin (β-hCG) level of 4950 mIU/ml, and transvaginal ultrasonographic identification of a 14 mm intrauterine sac with a corpus luteum on the left ovary. The next day (day 1), after written informed consent, she received 600 mg mifepristone orally. On day 4 she received 50 μg 15-methyl prostaglandin $F_{2\alpha}$ intramuscularly, also per protocol. Vaginal bleeding began on day 3 and decreased to light spotting on day 12. Serial β-hCG levels were monitored as follows: day 0, 4950; day 1, 7300; day 4, 5760; day

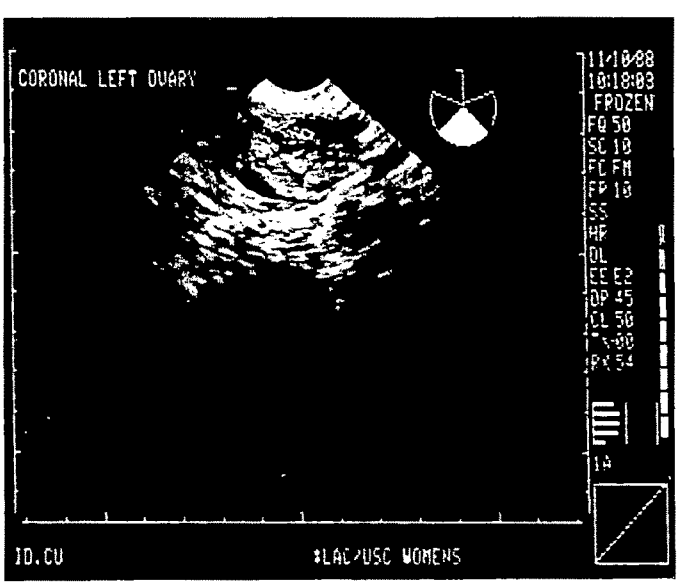


Fig. 1. Transvaginal ultrasonographic image of 12 × 4 mm irregular left ovarian cyst.

8, 1120; and day 14; 1690 mIU/ml. On day 14 the examination result was normal. Another examination on day 19 was also normal, but the β-hCG level had risen to 1930 mIU/ml. Curettage was performed on day 21 for removal of presumed retained products of conception. Vaginal ultrasonography before the curettage revealed no intrauterine sac, no corpus luteum, and no identifiable adnexal abnormality.

Although no villi were identified grossly or microscopically, the curettings contained intermediate trophoblastic tissue positive for keratin and placental lactogen, consistent with the diagnosis of residual intrauterine products of conception.[3] In addition, retrospective measurements of serum progesterone from day 0 and day 1 were 27.4 and 32.5 ng/ml, further corroborating the initial presence of an intrauterine pregnancy.[4]

After the curettage β-hCG levels decreased to 1180 mIU/ml (day 25) but then rose to 1840 mIU/ml (day 29). Repeat vaginal ultrasonography on day 29 revealed a flattened 12 × 4 mm irregular left ovarian cyst (Fig. 1). An ovarian ectopic pregnancy was suspected. Still asymptomatic, the patient was scheduled for laparoscopy that was performed later that day. Laparoscopy revealed normal fallopian tubes (including normal chromopertubation) and an unruptured left ovarian pregnancy. This ectopic pregnancy was removed laparoscopically after blunt dissection with grasping forceps and unipolar electrocautery of the crater deep within the ovary. The patient was discharged less than 12 hours after operation.

Microscopic examination of the tissue removed from the ovary confirmed the presence of chorionic villi with normal trophoblast. The patient recovered completely with β-hCG levels that decreased to 82 mIU/ml and then to undetectable levels by postoperative days 7 and 21, respectively.

Comment

The discovery of this ovarian pregnancy resistant to administration of mifepristone and prostaglandin supports previous findings that ectopic trophoblastic tissue may persist after such treatment. We believe that this case represents the first instance of the preoperative diagnosis of a spontaneously occurring, coexisting intrauterine and ovarian pregnancy in an asymptomatic patient. Finally, operative laparoscopy provided effective operative management of this early unruptured ovarian ectopic pregnancy.

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The impact of a quality assurance process on the frequency and confirmation rate of hysterectomy

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A criteria-based quality assurance process for hysterectomy was instituted at a large teaching hospital. After this process was initiated, the overall frequency of hysterectomy decreased by 24%, $p < 0.001$. Significant reductions were seen in hysterectomy rates for the following indications: chronic pelvic pain (77%, $p < 0.0001$), recurrent uterine bleeding (46%, $p < 0.001$), preinvasive disease of the uterus (55%, $p < 0.005$), and severe infection (70%, $p < 0.025$). Adenomyosis was the single indication for which an increase in hysterectomy rate was observed. This increase, however, was completely reversed during the last 2 years of the study. This quality assurance process also resulted in a significant increase in the histologic verification rate (i.e., 82% vs 93%, $p < 0.001$). These observations suggest that using such a criteria-based process can reduce the number of hysterectomies performed and improve the accuracy of the preoperative diagnosis. (Am J Obstet Gynecol 1990;163:545-50.)

Key words: Hysterectomy indications, quality assurance

The incidence of hysterectomy in the United States peaked in 1975 when an estimated 725,000 such procedures were performed. Since 1980 the estimated annual number (about 650,000) and rate of the procedure have not changed significantly.[1] Until recently, this figure was more than twice that reported in some Western European countries and currently remains one third higher.[2, 3] Regional rates for hysterectomy in the United States vary significantly, with rates highest in the South and lowest in the Northeast.[4, 5]

The lack of consensus concerning the acceptability of various indications for hysterectomy complicates efforts to determine which procedures are clearly appropriate. In addition, listing multiple indications for hysterectomy leads to confusion when others attempt to understand the primary reason for the procedure. Few reliable studies have been done that provide objective justification for many of the generally accepted indications for hysterectomy. One recent study reported that in 48% of hysterectomies reviewed, accuracy of the preoperative diagnosis could not be evaluated.[6] This difficulty arises because many appropriate indications for hysterectomy are not expected to be confirmed by abnormal tissue. For such indications suitable preoperative validation criteria are usually not provided.[4]

We recently reported a criteria-based quality assurance process that required the surgeon to select preoperatively a single indication for hysterectomy from a designated list of generally accepted indications.[7]

The purpose of this report is to examine the impact of this process on both the frequency and histologic verification rate of hysterectomy at a large military teaching hospital.

Methods

During the study period, from January 1984 through December 1987, surgeons were required to select preoperatively a single indication for each hysterectomy performed at San Diego Naval Hospital. The study protocol was reviewed and approved by the institutional review board. The specific criteria required in the preoperative evaluation of each patient have been reported previously[7] and are listed in Table I. When pathologic tissue was expected in the surgical specimen, the indication could be *verified** by the pathology report. When no pathologic tissue was expected, the indication could be *validated*† if the surgeon's preoperative note

*Used throughout this article to refer to indications that should be confirmed by histologic-pathologic examination.

†Used throughout this article to refer to indications that should be confirmed by documentation in the surgeon's preoperative note of criteria to be met before the performance of a hysterectomy.

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Table I. Hysterectomy indication list with criteria

Acute condition	
A-1*	Pregnancy catastrophe (e.g., severe hemorrhage)
A-2	Severe infection (e.g., ruptured tuboovarian abscess)
A-3*	Operative complication (e.g., uterine perforation)
Benign disease (pathologic tissue expected)	
B-1	Leiomyoma
	a. Symptomatic (e.g., bleeding, pressure)
	b. Asymptomatic (>12 wk size, confuses adnexal evaluation)
B-2	Endometriosis (distinct endometriosis, unresponsive to hormone suppression or conservative surgery)
B-3	Adenomyosis
B-4	Chronic infection (e.g., recurrent pelvic inflammatory disease)
B-5	Adnexal mass (e.g., ovarian neoplasm)
B-6	Other (operator-defined, criteria specified)
Cancer or significant premalignant disease	
C-1	Invasive disease of reproductive organs
C-2	Significant preinvasive disease of uterus (high-grade squamous intraepithelial lesion or adenomatous hyperplasia of endometrium with cellular atypia)
C-3	Cancer of adjacent or distant organ (gastrointestinal, genitourinary, or breast cancer)
Discomfort (no pathologic tissue expected)	
D-1*	Chronic pelvic pain (negative laparoscopy and nonsurgical treatment attempted)
D-2*	Pelvic relaxation (symptomatic)
D-3*	Stress urinary incontinence (positive urodynamic workup)
D-4*	Recurrent uterine bleeding (unresponsive to hormone regulation and curettage—normal-sized uterus)
D-5*	Other (operator-defined, criteria specified)
Extenuating circumstances (not specifically indicated but possibly justified—requires preoperative peer review)	
E-1*	Sterilization (extenuating circumstances)
E-2*	Cancer prophylaxis (e.g., recurrent high-grade squamous intraepithelial lesion after cone biopsy or persistent adenomatous hyperplasia of endometrium without atypia)
E-3*	Other—listing extenuating circumstances

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*Denotes indications where pathologic tissue is not expected to confirm the preoperative diagnosis.

documented that certain criteria had been satisfied. After the quality assurance process was initiated, frequent feedback regarding the rates of verification and validation of preoperative diagnoses was provided to medical staff members. This information was updated at least every 6 months and made available at weekly preoperative conferences.

To compare the cumulative frequency of hysterectomy before and after the quality assurance process, the charts of all patients who underwent hysterectomy at San Diego Naval Hospital from July 1981 through December 1983 were reviewed. Before July 1981, reliable data regarding hysterectomy indications were not available. The listed indication for each hysterectomy was determined. During this control period there was no designated list from which a specific indication for each hysterectomy could be selected. In those instances when more than one indication was listed, the first indication was assumed to be the primary one. These hysterectomies with multiple indications accounted for 92 (14%) of the 657 hysterectomies performed during this control period. The number of hysterectomies performed in each year of the study and control periods and the number of admissions to the gynecology service for the same years were tabulated. The cumulative frequency of hysterectomy was calculated by dividing the number of hysterectomies by the number of admissions to the gynecology service during the same time period and multiplying by 100. This is expressed as a rate per 100 gynecology admissions.

Review of admission policy, age, race, and active duty military status during both periods revealed no factors that might have caused significant differences in the demographic profile of patients admitted to the gynecology service. Also, the number of health-care providers, as well as the number of available operating rooms, was unchanged during both periods. Before initiating the quality assurance process in 1984, operating surgeons were unaware of the plans to implement such a program. A military hospital, as a study institution, is unique because the catchment areas for patient eligibility are well defined and policies regarding patient care are more constant than for other types of hospitals.

Statistical analysis of the hysterectomy rates by indication during each of the two periods was performed with either χ^2 or two-tailed Fisher's exact test as appropriate. A confidence level of $p < 0.05$ was considered significant. To assess whether any observed change in the cumulative frequency of hysterectomy was due to

Table II. Hysterectomy indication profile and incidence before and after initiation of the quality assurance process

Indication	Control period (July 1981–Dec. 1983)			Study period (Jan. 1984–Dec. 1987)			p Value†
	No.	%	Rate*	No.	%	Rate*	
Acute condition							
A-1 Pregnancy catastrophe	4	1	0.08	16	2	0.22	NS
A-2 Severe infection	13	2	0.27	6	1	0.08	<0.025
A-3 Operative complication	0	0	0	0	0	0	NS
Benign disease							
B-1 Leiomyoma	133	20	2.74	226	30	3.10	NS
B-2 Endometriosis	16	2	0.33	17	2	0.23	NS
B-3 Adenomyosis	5	1	0.10	33	4	0.45	<0.005
B-4 Chronic infection	13	2	0.27	19	2	0.26	NS
B-5 Adnexal mass	57	9	1.17	75	10	1.03	NS
B-6 Other	1	<1	0.02	0	0	0	NS
Cancer or premalignant disease							
C-1 Invasive cancer	67	10	1.38	85	11	1.17	NS
C-2 Preinvasive disease	41	6	0.84	28	4	0.38	<0.005
C-3 Adjacent or distant cancer	0	0	0	1	<1	0.01	NS
Discomfort							
D-1 Chronic pelvic pain	125	19	2.57	43	6	0.59	<0.0001
D-2 Pelvic relaxation	47	7	0.97	76	10	1.04	NS
D-3 Stress urinary incontinence	45	7	0.93	46	6	0.63	NS
D-4 Recurrent uterine bleeding	86	13	1.77	69	9	0.95	<0.001
D-5 Other	0	0	0	0	0	0	NS
Extenuating circumstances							
E-1 Sterilization	1	<1	0.02	3	<1	0.04	NS
E-2 Cancer prophylaxis	3	<1	0.06	5	<1	0.07	NS
E-3 Other	0	0	0	0	0	0	NS
TOTAL	657	100	13.5	748	100	10.3	<0.001

*Per 100 gynecologic admissions.
†χ^2 or two-tailed Fisher's exact test as appropriate.

the quality assurance process or was simply the result of an unrelated gradual decrease over the 78-month time frame (control and study periods combined), a time series analysis[8] of the quarterly rates of hysterectomy during the control period was compared with a time series analysis of the quarterly rates during the study period.

Results

A total of 657 hysterectomies were performed between July 1981 and December 1983, and 748 were performed between January 1984 and December 1987. The average quarterly admission rate for the 30-month control period, when there were 4860 admissions to the gynecology service, was 487 ± 49. This rate did not differ significantly from that of the 48-month study period (455 ± 80) when there were 7280 admissions ($p = 0.56$).

A significant reduction ($p < 0.001$) in the overall hysterectomy rate was observed during the study period (Table II). Significant decreases in the rates of hysterectomy for chronic pelvic pain ($p < 0.0001$), recurrent uterine bleeding ($p < 0.001$), preinvasive disease of the uterus ($p < 0.005$), and severe infection ($p < 0.025$) were observed during the study. Adenomyosis was the only indication for which a statistically significant increase in the hysterectomy rate was observed ($p < 0.001$).

After we instituted the quality assurance process, a significant decrease in the hysterectomy rate was seen for those indications where pathologic tissue was not expected (6.5 vs 3.5 per 100 gynecology admissions, $p < 0.001$). This group of indications consisted of pregnancy catastrophe, operative complication, chronic pelvic pain, stress urinary incontinence, recurrent uterine bleeding, and those elective hysterectomies done with extenuating circumstances. Also observed was a significantly higher percentage of verifiable indications that were confirmed after initiation of the quality assurance process (282 of 345 or 82% vs 459 of 494 or 93%, $p < 0.001$). Table III lists these indications with verification rates before and after the quality assurance process.

Linear regression analysis of the quarterly hysterectomy rates before and after initiation of the quality assurance process are shown in Fig. 1. This time series analysis of the rates indicates no significant upward or downward trend within either the control period or the

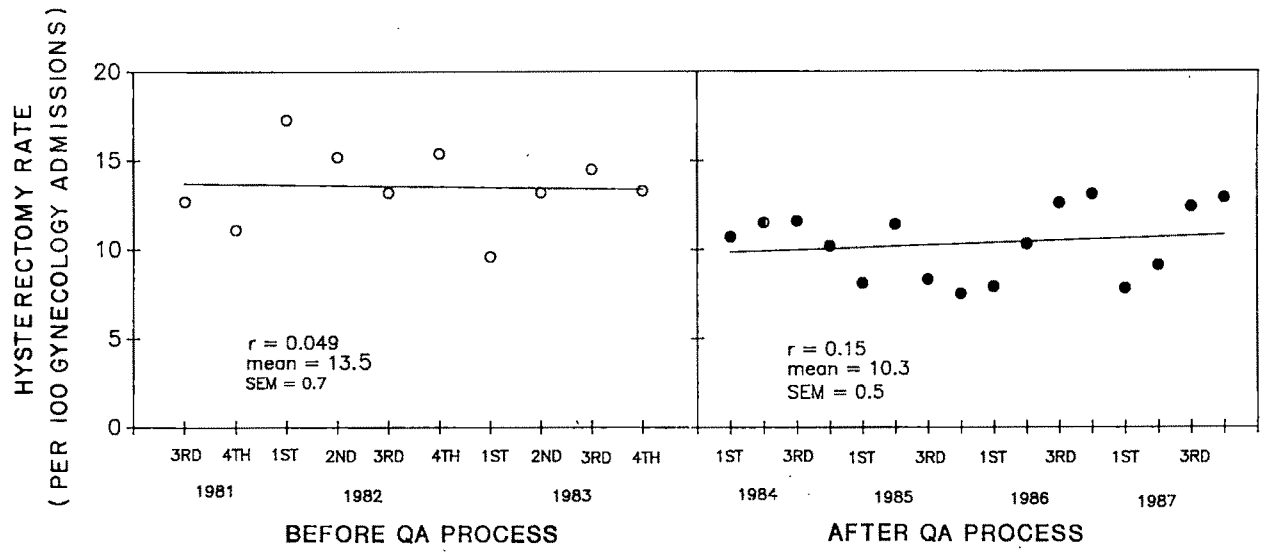


Fig. 1. Time series analysis of quarterly hysterectomy rates before *(open circles)* and after *(closed circles)* the quality assurance process. The significant decrease in mean cumulative incidence (13.5 vs 10.3, $p < 0.001$) is not a gradual decline over time but rather a discrete change that occurs after institution of the quality assurance process in January 1984.

Table III. Number and percent of surgical specimens by indication for hysterectomy that were confirmed by pathologic tissue (verified) before and after the quality assurance process*

Indication	*Before quality assurance process*		*After quality assurance process*		*p Value†*
	No.	*%*	*No.*	*%*	
Severe infection	10/13	77	6/6	100	NS
Leiomyoma	113/133	85	217/230	94	<0.001
Endometriosis	8/16	50	15/17	88	<0.05
Adenomyosis	2/5	40	13/33	38	NS
Chronic infection	8/13	62	19/19	100	<0.05
Adnexal mass	39/57	68	75/75	100	<0.001
Invasive cancer	67/67	100	85/85	100	NS
Preinvasive cancer	35/41	85	28/28	100	NS
Adjacent cancer	0	0	1/1	100	NS
	282/345	82	459/494	93	<0.001

*Before process 345 of 657 or 52% were potentially verifiable versus 494 of 748 or 66% after the quality assurance process ($p < 0.01$).

†χ^2 or two-tailed Fisher's exact test as appropriate.

study period even though the overall rate of hysterectomy was significantly lower during the entire study period (10.3 per 100 admissions) than during the entire control period (13.5 per 100 admissions). These data suggest that the observed decrease in overall hysterectomy rate was the result of the quality assurance process rather than the result of a gradual downward trend over time.

Comment

The basis for the relatively high incidence of hysterectomy in the United States has been scrutinized by a variety of medical and nonmedical authorities.[9-11] Regional differences in the incidence of this procedure have been cited as evidence that the overall number could be significantly reduced.[4,5] One study has shown that requiring the use of a generally accepted list of indications for hysterectomy can result in a decrease in its incidence.[12] This study supports this concept by demonstrating a 24% reduction in the incidence of hysterectomy after institution of a criteria-based quality assurance process.

By requiring the surgeon to select a single indication the process was easily monitored and the reason for individual hysterectomies was clarified. Listing multiple indications has been recognized previously as a source

of confusion and may encourage the practice of adding together several insufficient indications to justify the surgery.[13]

Clarification of the reasons for surgery and feedback of information about therapeutic outcome to both physicians and the public have been reported to reduce both the incidence and the regional variation of several surgical procedures including hysterectomy.[14, 15]

Comparison of hysterectomy rates before and after initiation of the quality assurance process shows that significant decreases occurred for several of the more ambiguous and controversial indications.[6, 7, 13] Chronic pelvic pain accounted for the largest decrease (77%) in the rate of hysterectomies performed. The requirement of prior diagnostic laparoscopy and the option of alternative management in a multidisciplinary chronic pelvic pain clinic, which was established as part of the quality assurance program, may have reduced the need for hysterectomy as other treatment modalities, such as psychiatric and pharmacologic therapy, were found to be effective alternatives.

Recurrent uterine bleeding was another indication for which a substantial decrease in hysterectomy incidence was noted. The requirements of a trial of hormonal therapy and at least one uterine curettage may explain the 46% decrease in hysterectomy rate for this indication. Long-term follow-up will be required to ascertain if these alternative therapies done in cases of chronic pelvic pain and recurrent uterine bleeding merely delayed, rather than eliminated, the performance of a hysterectomy.

The 55% decrease in the rate of hysterectomy for treatment of preinvasive disease of the uterus was probably caused by the fact that after initiation of the quality assurance process, only "significant" premalignant lesions of the cervix or the endometrium, such as severe cervical dysplasia or adenomatous endometrial hyperplasia with cellular atypia, were considered to be acceptable indications.

Adenomyosis was initially selected more frequently as a preoperative indication for hysterectomy after establishing the quality assurance protocol. This effect most likely occurred because the criteria for chronic pelvic pain (Table I, D-1) or recurrent uterine bleeding (Table I, D-4) required more extensive and specific preoperative evaluation than did adenomyosis. However, the rate of hysterectomy because of adenomyosis dropped significantly during the second 2 years of the study as compared with the first 2 years (0.7 vs 0.2 per 100 gynecology admissions, $p < 0.01$). Presumably this was due to the low rate of histologic verification (38%) observed and reported for this indication during the first 2 years of the study. Currently, at our institutions adenomyosis is not considered to be a reliable preoperative indication for hysterectomy.

Another important finding was the decreased frequency with which "validatable" indications (no pathologic tissue expected) were chosen during the study period (6.5 vs 3.5 per 100 gynecology admissions). This could be explained by the fact that some of the preoperative validation criteria included certain therapeutic modalities (e.g., curettage, trial of hormones, laparoscopy, and pelvic pain clinic). Many patients could have experienced symptomatic relief as a result of these alternative interventions and the need for hysterectomy could have been avoided. Again, follow-up studies will be needed to confirm this impression.

Also noted was a significant increase in the histologic verification rate after initiation of the quality assurance process. This would imply that a quality assurance program with timely feedback of information may also improve diagnostic accuracy.

We realize that improvement in the confirmation rate of the indication does not by itself provide justification for any surgery performed. Stress urinary incontinence, where abnormal uterine tissue is not expected, is an excellent example of an indication that may have been validated preoperatively for this study but for which hysterectomy is probably not a necessary component of the therapy. Recent investigations have demonstrated similar therapeutic outcomes when urethropexy was performed without hysterectomy.[16, 17]

Long-term outcome for each indication for hysterectomy should be compared to alternative forms of therapy, both surgical and nonsurgical, with respect to efficacy, safety, and cost.[18] We feel that the consistent application of a quality assurance process such as this could very likely encourage the evolution of a standardized indication list with concomitant confirmation criteria for each indication. This would greatly facilitate the comparison of the effectiveness and appropriateness of the various therapies for each indication. As information is collected and analyzed, it may be logical to consider eliminating certain indications from the list, as in the case of adenomyosis and urinary stress incontinence.

The results of this study suggest that a quality assurance process that required the selection of a single preoperative indication from a standardized list of indications, and which establishes specific preoperative validation criteria for those cases when pathologic tissue is not expected, may be a substantial factor in reducing the frequency of hysterectomy. Because this study is a single-hospital-based analysis with the number of gynecology admissions used as the denominator to calculate the rate of a procedure, these changes could have been influenced by differences in types of patients admitted or surgeons operating during the two periods that were analyzed. These differences are less likely to have occurred at a stable military hospital, however,

and it is unlikely that the substantial (24%) decrease could be explained on this basis alone.

The results of this study also show that frequent feedback at weekly preoperative conferences of confirmation rates does result in an improvement in the diagnostic accuracy of the preoperative diagnosis (indication) for hysterectomy. This finding is not likely to have been influenced by the methods of this study.

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Retropubic long-needle suspension procedures for stress urinary incontinence

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A brief review of the Pereyra and the Stamey procedures and their modifications, including success rates and potential problems, is presented. A new modified technique is described that has potential advantages of ease, rapidity, less dissection, and less blood loss than may be seen with the modified Pereyra procedure and less chance of foreign body reaction than may be seen with the Stamey procedure. Twenty patients with significant stress urinary incontinence (14 with concurrent severe pelvic relaxation) underwent the procedure with an 80% cure plus 5% significant improvement rate noted 12 to 39 months after operation. All failures occurred in patients who were obese and involved apparent suture pull-through. Complications were minimal. Suggested causes for failures are discussed. (Am J Obstet Gynecol 1990;163:551-7.)

Key words: Stress urinary incontinence, Pereyra procedure, Stamey procedure, Raz procedure, Gittes procedure

A number of gynecologists and urologists have promoted a variety of procedures for anatomic stress incontinence that involve the retropubic passage of long suture-loaded needles. These procedures have been advocated because of their "relative ease," presumed shorter operative times, and lower perioperative morbidity than the abdominal retropubic suspensions, and for their potential use with vaginal repair procedures in patients with significant pelvic relaxation and concurrent severe stress urinary incontinence.

In 1959, 10 years after the first Marshall-Marchetti-Krantz description was published, Pereyra[1] described his first procedure that used a specially designed two-pronged needle, stainless steel wire, and a small suprapubic abdominal incision down to but not including the rectus fascia. Subsequent modifications of the procedure have included blunt retropubic dissection and the use of a pubourethral helical stitch of permanent suture to prevent technique failure caused by suture pull-through.[2,3] Stamey,[4-6] Raz,[7] Leach and Raz,[8] Muzsnai et al.[9], and others[10-12] have reported other modifications or somewhat similar procedures to both simplify stitch placement and to better secure the elevating sutures. Reported cure rates have varied with technique and with the type and duration of patient follow-up (Tables I and II). Although complications appear to be rare with the Stamey procedure, the incidence of delayed suture reaction or chronic pain in the area of the periurethral buttress appears to be significant. In addition, the operative times and perioperative blood loss with these modified Pereyra procedures may be comparable to those observed with abdominal approaches. Recently Gittes and Loughlin[18] described a more simplified procedure in which no vaginal incision and only stab suprapubic incisions are made. Although the initial success rate of this procedure may be acceptable, it has been suggested that long-term success will be poor as a result of suture pull-through.

Several further modifications of these techniques have been made after consideration of the actual and theoretical advantages and disadvantages of the procedures.

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Material and methods

Operative technique. A transverse incision approximately 5 cm in length is made 2 cm above the symphysis pubis to the rectus fascia. An area of the fascia approximately 3 × 5 cm is cleaned. If an anterior colporrhaphy is to be performed for a symptomatic cystocele, the anterior vaginal midline incision is stopped 2 cm proximal to the bladder neck. A transverse vaginal incision is made through the submucosa 1 cm distal to

Table I. Modified Pereyra procedure—Results

Study	*No. of patients*	*Follow-up*	*Success (%)*	*Complications*
Raz[7] (1981)	100	Not included	96	1 Bladder perforation 1 Hemorrhage necessitating transfusion 2 Skin infections
Pereyra et al.[3] (1982)	54 Primary procedure	4-6 yr	87 (Cured) 7.4 (Improved)	29 Urinary tract infections 2 Outlet obstructions
	28 After previous failed incontinence procedures	4-6 yr	82 (Cured) 7 (Improved)	
Muzsnai et al.[9] (1982)	98 More extensive procedure with multiple sutures	6-36 mo	95	11 Wound infections
Leach and Raz[8] (1984)	54 After previous failed incontinence procedures	>2 yr	94	Not included No fistulas
Bhatia and Bergman[13] (1985)	20	1 yr (objective)	85	Minimal
Pow-sang et al.[14] (1986)	20 With pure stress urinary incontinence	6-27 mo	91	1 Suture abscess

Table II. Stamey procedure—Results

Study	*No. of patients*	*Follow-up*	*Success (%)*	*Complications*
Stamey[5] (1980)	203	6 mo–4 yr	91	Suture reaction 3%
Mundy[15] (1983)	25	1 yr (Subjective & objective)	84 (Cure of stress urinary incontinence)	Suture reaction 28% Prolonged voiding dysfunction 24%
Ashken et al.[16] (1984)	60	1-3 yr	84 (Cure) 5 (Improved with persistent urge incontinence)	Suture reaction 5%
Richardson et al.[17] (1984)	163	3 yr	92	Suture reaction 5%
Pow-sang et al.[14] (1986)	19	6 mo–1 yr	74	Suture reaction 12%

the bladder neck. Scissors are then inserted with spreading deep to the vaginal submucosa (paravaginal fascia) on each side of the bladder neck to dissect two areas 1.5 to 2 cm diameter between the paravaginal fascia and the pubourethral connective tissue (Fig. 1). The paravaginal connective tissue and vaginal submucosa is then incorporated in two to three needle bites with a no. 1 Teflon-coated nylon suture (1 Ti-cron [DT-19], Davis and Geck, Dansbury, Conn.) on a genitourinary type needle (Fig. 2). If the overlying pubourethral connective tissue appears dense, it is incorporated in one of these bites. Suture placement should always be lateral to the urethral-vesical junction. Preoperative estrogen administration (preferably for 3 months) to improve tissue strength appears to be important in patients with vaginal atrophy. If the patient

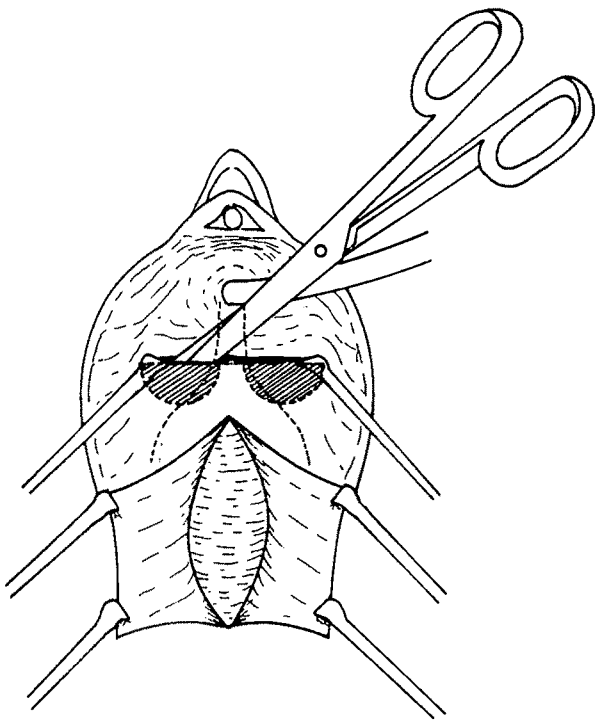


Fig. 1. Modified procedure. Dissection is performed deep to the paravaginal connective tissue, bilaterally, through a transverse incision 1 cm distal to the bladder neck.

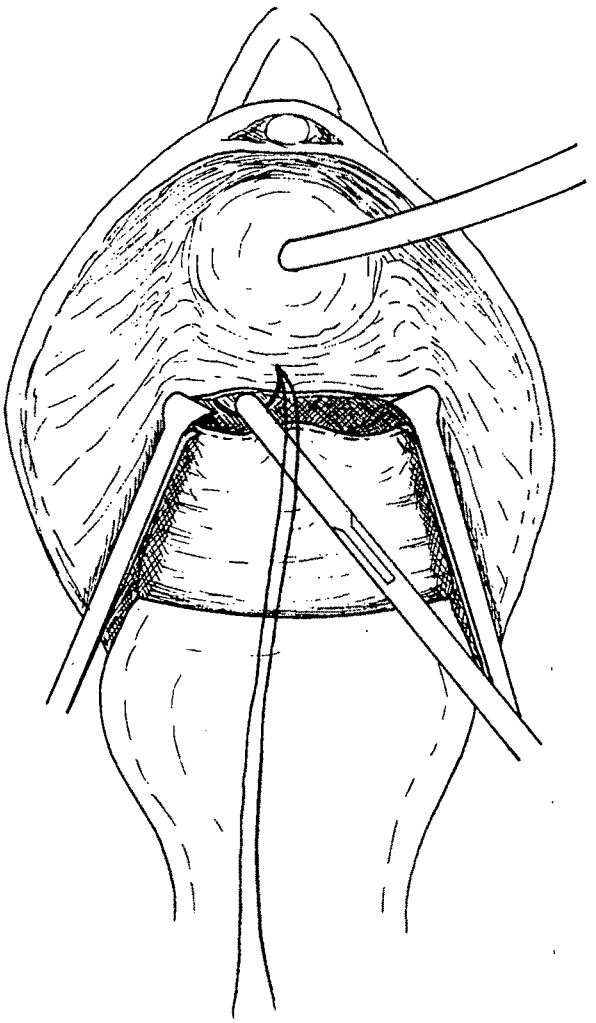


Fig. 2. Permanent no. 1 nylon sutures (three needle bites) are placed into the paravaginal connective tissue (often full-thickness) lateral to the bladder neck.

has had a previous retropubic procedure or has evidence of anterior vaginal or bladder neck scarring, more extensive lateral and subpubic dissection is performed to mobilize the bladder neck, proximal urethra, and underlying vagina to avoid excess tension at the suture sites.

A Stamey needle is then loaded with the free end of the suture with its origin closest to the bladder neck. It is placed an estimated 1 cm lateral to the Foley bulb just proximal to the urethral-vesical junction. After complete bladder emptying is noted, the needle is then directed anteriorly and advanced until the resistance of the symphysis pubis is met, then shifted anteriocephalad to pass retropubically through the cleaned area of rectus fascia where the suture is removed from the needle (Fig. 3). The needle is then removed and reloaded with the lateral free suture end. It is placed 1.5 cm lateral and distal to the first and advanced likewise retropubically to the fascia 1 to 2 cm lateral to the first suture. The same procedure is done on the opposite side of the bladder neck.

At this point in the procedure a 70-degree cystoscope is placed transurethrally, and, while filling, the bladder is examined for evidence of suture. If a perforation is noted, the suture is removed, the bladder is emptied, and the suture is replaced. Before removal of the cystoscope, bladder neck closure is observed by elevating the suture ends above the abdominal incision.

Before elevation of the retropubic sutures the anterior colporrhaphy is completed, the vaginal incisions are closed, and a suprapubic catheter is placed. The sutures are then elevated and secured above the rectus fascia (Fig. 4). When the rectus fascia is noted to be thin and attenuated, a small Gore-Tex patch (W. L. Gore & Associates, Inc., Elkton, Md.) is used above the fascia to prevent potential suture pull-through. The amount of elevation of the bladder neck is a matter of judgment and depends on the severity of the defect, cystoscopic evidence of bladder neck closure with suture elevation, and whether leakage can be produced by suprapubic pressure on the full bladder. After tying

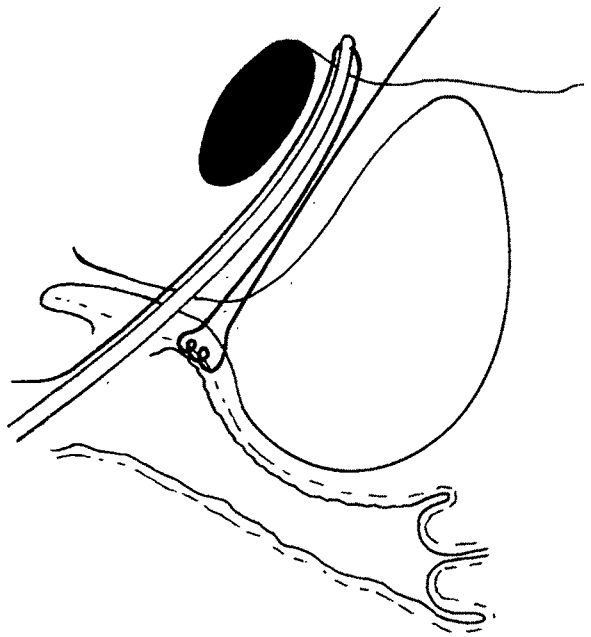


Fig. 3. The suture-loaded Stamey needle is passed twice on each side of the bladder neck through the vaginal incision, pubourethral connective tissue, retropubic space, then rectus fascia.

the sutures the abdominal wall incision is then thoroughly irrigated and closed.

Prophylactic antibiotics are given perioperatively and estrogen therapy is continued postoperatively in menopausal patients.

Evaluations and patient characteristics. This procedure was performed on 20 patients between September 1985 and December 1987. The author was the primary surgeon for all of the cases. Patient evaluation before surgery included (1) history and physical examination (a thorough urologic history and pelvic examination were performed noting pelvic relaxation and bladder neck descent with Valsalva in the lithotomy and standing position and perineal neurologic function), (2) urinalysis, urine culture, or both, (3) urodynamic assessments that included a flow study, residual urine measurements, resting urethral pressure profile with a dual-microtip transducer catheter, water cystometrics, stress tests, and voiding studies, (4) dynamic urethroscopy, and (5) voiding cystourethrograms in two patients with unusual symptoms.

Patients ages ranged from 38 to 71 years (mean, 59; median, 56). Fifteen of the patients were menopausal and 12 of these received preoperative estrogen therapy. Twelve patients were multiparous and there were no nulliparous patients.

All patients related urine loss with coughing, laughing, and physical activity. Only five of the 20 patients did not use protective clothing or pads and each of these had third- or fourth-degree cystoceles and experienced significant stress leakage when the prolapse was reduced. One patient had constant leakage, a very low-pressure urethra, and declined a sling procedure. Past history revealed six patients with failure of previous surgery for stress incontinence. Fourteen patients had previous hysterectomies. Medical problems included three patients with chronic obstructive pulmonary disease, three with severe arthritis, and one with coronary artery disease after coronary bypass. Nine of the patients were smokers. Patient weights ranged from 104 to 250 pounds (mean weight, 166 pounds; median, 167 pounds). Seventy percent of the patients could be defined as obese (>120% of their ideal body weight by Metropolitan Life Tables, 1959); 14 patients weighed >145 pounds, eight weighed >180 pounds, and three weighed >220 pounds. Fourteen patients (70%) had concurrent pelvic relaxation, four with either total vault prolapse or procidentia. Six of the patients (three elderly and two morbidly obese) required an incontinence procedure alone and chose the procedure over a retropubic approach.

Bladder evaluations revealed that all patients had positive stress tests before capacity and urodynamic evidence of stress incontinence. Five patients had peak urethral pressures <40 mm Hg (one with 10 mm Hg). Three patients had evidence of instability on cystometric evaluation; two had detrusor contractions only after positive stress tests. Eleven patients with cystoceles had intermittent flow on voiding study.

The procedure on all 20 patients was that described with the addition of anterior and posterior repair with sacrospinous vault suspension in three cases, vaginal hysterectomy with anterior and posterior repair (one with sacrospinous suspension) in three cases, anteroposterior repair in six cases, one anterior repair, and one posterior repair.

Telephone follow-up was obtained on all patients in December 1988 (12 months to 39 months after operation). All patients who complained of any leakage and six of the patients who reported having no leakage with stress underwent urodynamic evaluation after December 1988.

Results

Sixteen patients (80%) reported complete relief of leakage with stress. Six of these 16 underwent examination and urodynamic evaluation that confirmed operative success. One of the 16 related rare leakage with urgency when her bladder was full and had detrusor instability confirmed urodynamically before and after

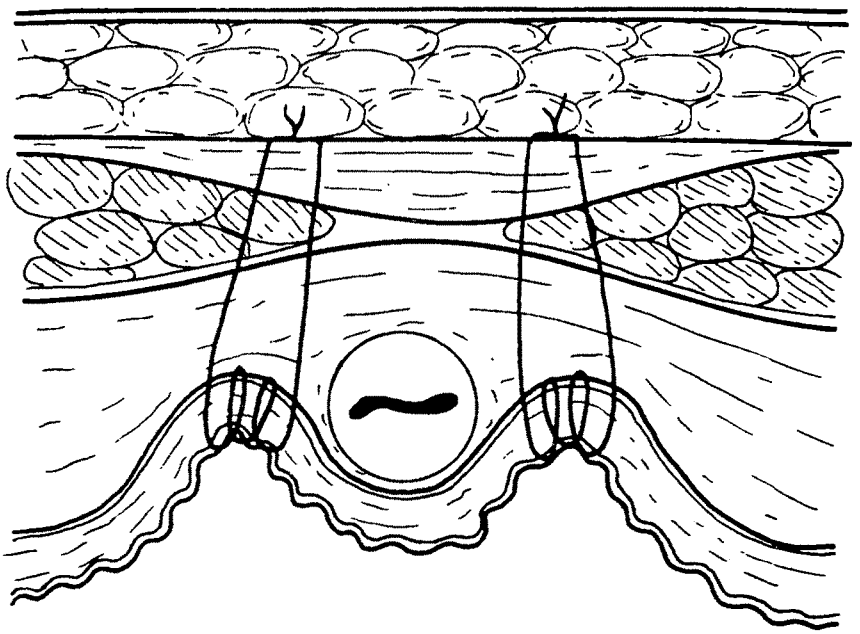


Fig. 4. After cystoscopy, the sutures are secured to the rectus fascia, thus elevating the urethrovesical junction.

operation. One patient whose weight increased from 220 to 280 pounds since operation in June 1986 had improvement but had some recurrence of stress incontinence beginning 1 year after operation. The overall cure and improvement rate was 85%. No failures occurred in patients who had undergone previous operation for stress incontinence.

The procedure failed in three patients (recurrence of stress incontinence) at 4 weeks, 4 months, and 14 months after operation. All three had recurrence of bladder neck descent, positive stress tests, and positive dynamic urethral pressure profiles when evaluated. All were obese (189, 228, and 250 pounds). The patient with early failure weighed 189 pounds, was a heavy smoker, had an atrophic vagina at the time of operation, and resumed manual work 4 weeks after operation.

Complications included one small subcutaneous hematoma, one retropubic hematoma responsible for a four-point hematocrit drop that did not necessitate transfusion, three postoperative urinary tract infections during suprapubic drainage, and one unilateral stitch reaction that was noted 4 months after operation. The stitch was removed and the patient has remained continent and without other symptoms. There have been no fistulas or patients with chronic retropubic pain.

Suprapubic bladder drainage was used until patients were able to empty 75% of their bladder volume with less than 75 ml of residual urine. Only three patients voided adequately within 5 days of the procedure. The median voiding time was 10 days. Two patients required 21 days; however, all related no voiding difficulty when questioned.

The hospital stays of patients who had the procedure with concurrent repairs ranged from 3 to 6 days (mean, 4.9 days; median, 5 days). The six patients who had only needle suspension procedures had hospital stays ranging from 2 to 4 days (mean, 3.1 days.) The mean stay for patients undergoing abdominal retropubic suspension at the same institution is 5.5 days.

Comment

It is generally accepted that stress urinary incontinence results from changes in proximal urethral mechanics. All known surgical procedures for this problem have devised means whereby the urethral pressure increases with increases in intraabdominal pressure. The retropubic needle suspensions that include this relatively easily performed procedure appear to effectively create this situation. The theoretical advantages of this procedure are (1) that it is performed more rapidly than either Stamey or Pereyra procedures, (2) that there is relatively less dissection and less blood loss than with a modified Pereyra procedure, (3) that the needles are placed more easily vaginally with direct observation or palpation of the bladder neck, and (4) that, as with the most recent modification of the Pereyra procedures, the paravaginal connective tissue is the pri-

mary tissue that is elevated. Because of the complete dissection of the abdominal rectus fascia suture pull-through is thought to be less of a problem than may be seen with Gittes modification.

Although abdominal approaches may be used in patients with combined significant stress urinary incontinence and pelvic relaxation, vaginal approaches with slightly shorter hospital stays and possibly lower perioperative morbidity definitely are options. Some have advocated the pubourethral stitch anterior repair for these situations; however, others[19] have found unacceptable failure rates and have recommended alternative means of elevating the bladder neck. Combined vaginal repair procedures and long-needle suspensions should be considered.

The success rates seen in this small series with somewhat short follow-up and in some of the other needle suspension series are not quite comparable to those reported with abdominal-retropubic suspensions (85% to 95%). However, some of the differences in success may be related to the type of patients who have the procedures. For instance, a greater percentage of the long needle suspension procedures may have been performed in menopausal, obese patients with medical problems in whom laparotomy might produce a higher complication rate. Clearly, obesity was a common factor in all failures in this small series. The failure rate for the women weighing over 220 pounds was 100% (0% for nine women weighing less than 180 pounds). A well-controlled comparison of approaches in both obese and patients with normal weights is needed.

Each failure in this small series was associated with recurrence of descent of the urethral-vesical junction after successful surgical elevation. Each patient was continent for a period of time after operation. It is presumed that the procedures failed because the permanent suture material pulled through or became detached from either the vaginal submucosa or the rectus fascia. It has been postulated that retropubic procedures have lower failure rates because retropubic scarring after dissection may further serve to fix the urethral-vesical junction. Factors that would seem to predispose to stitch pull-through are genital atrophy, scarring and tissue immobility, obesity, and other conditions associated with increased intraabdominal pressure and pelvic floor stress. Whether a retropubic procedure or perhaps a sling procedure is warranted in patients who have a higher risk of failure is certainly debatable.

The long-term complication rate in patients who have needle suspension procedures appears to be comparable with that seen with retropubic suspensions. The most prevalent complication appears to be retropubic pain and stitch infection or rejection. Although this problem is more prevalent in patients who have Stamey procedures with a permanent buttress material, the fact that this complication occurred in one of 20 patients in this series without buttresses remains somewhat worrisome. Subsequent experience with 20 more procedures has thus far revealed no similar problems. Postoperative urinary retention may occur for longer periods than with some retropubic procedures; however, this decreases with operator experience. Should long-term retention occur, the removal of one stitch has been shown to relieve the problem without recurrence of incontinence. Less bladder neck elevation may serve to prevent postoperative retention and decrease the potential for future stitch pull-through by decreasing the tension on the suture.

In summary, retropubic needle suspensions provide another alternative approach to the patient with anatomic urinary incontinence. The advantages of these procedures include relative ease and decreased perioperative pain and disability. Associated problems with the procedure include stitch rejection, problems associated with improper stitch placement, and failure rates that may be slightly higher than those seen with retropubic procedures. The described modified procedure offers a simple technique that can be performed rapidly with apparently little morbidity and rapid recovery. Long-term success with a greater number of patients remains to be evaluated.

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Ductus arteriosus flow velocity modulation by fetal breathing movements as a measure of fetal lung development

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A test is needed that would accurately predict favorable neonatal lung performance in the presence of prolonged severe oligohydramnios caused by ruptured membranes so that optimal obstetric care can be provided. We propose such a test that is based on the degree of modulation of fetal ductal blood flow velocity by fetal breathing movements after maternal glucose loading. In a prospective cross-sectional study of 49 normal pregnancies (50 fetuses) between 25 and 38 weeks an exponentional increase in breathing-related ductal blood flow velocity modulation was observed with advancing gestational age, reflecting the developing pulmonary vascular bed. Fetal ductal flow velocity waveforms were also recorded in 13 cases of prolonged severe oligohydramnios after ruptured membranes before 28 weeks' gestation. Normal ductal blood flow velocity modulation values were associated with normal neonatal lung performance, whereas reduced ductal blood flow velocity modulation values were associated with pulmonary hypoplasia. Fetal breathing-related ductal flow velocity modulation appears to be a promising predictor of neonatal lung performance. (Am J Obstet Gynecol 1990;163:558-66.)

Key words: Ductus arteriosus, Doppler flow velocity, fetal breathing movements, lung development

Rupture of membranes resulting in prolonged severe oligohydramnios during the second trimester of pregnancy may result in stillbirth or severe neonatal respiratory failure as a result of pulmonary hypoplasia. However, under these circumstances fetal outcome is not uniformly poor.[1] There is therefore a need for a test to accurately predict a favorable fetal outcome so that optimal obstetric care can be provided for these particular pregnancies.

In cases of prolonged severe oligohydraminos, contradictory findings have been reported with regard to the association between fetal breathing movements and lung performance after birth. According to Blott et al.[2] the predictive value of the presence of fetal breathing movements for continuing lung growth is 100%, and the predictive value of the absence of fetal breathing movements for pulmonary hypoplasia is 100%; however, Moessinger et al.[3] reported that the observation of fetal breathing activity is not helpful in identifying those fetuses with pulmonary hypoplasia at birth.

Ductal blood flow in the fetal lamb is modulated by lung expansion.[4] This effect results from an opening of the pulmonary vascular bed with subsequent reduced shunting of right ventricular output through the ductus arteriosus. Furthermore, increased pulmonary perfusion has been established with advancing gestational age, reflecting developing pulmonary vasculature.[5] In pulmonary hypoplasia the development of fifth- and sixth-generation vessels is impaired with a resultant reduction in development of the pulmonary vascular bed.[6] Moreover, pulmonary vascular resistance is raised and is associated with medial muscular hypertrophy of lung arterioles.[6] It may be speculated that fetal breathing-related modulation of ductal flow will be reduced in this situation.

Recently a pulsed Doppler method was introduced for recording blood flow velocity waveforms in the human fetal ductal arteriosus.[7] In this study the following questions were addressed. Does breathing-related modulation of ductal flow occur in the human fetus? If so, is this modulation age dependent and is the presence of breathing-related ductal flow modulation in prolonged severe oligohydramnios caused by ruptured membranes indicative of absent pulmonary hypoplasia?

Material and methods

All women gave informed consent for the study, which was approved by the Ethics Review Board of the University Hospital. The gestational age was calculated from a reliable menstrual history and ultrasonographic measurement of fetal crown-rump length or biparietal diameter. All women were nonsmokers.

The study population consisted of two groups. The

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first group represented 55 uncomplicated pregnancies with a mean gestational age of 32.3 weeks (range, 25 to 38 weeks) randomly selected at the outpatient clinic between August 1988 and March 1989 for a cross-sectional study of normal breathing-related fetal ductal peak systolic flow velocity modulation. Recordings were performed from 25 weeks of gestation because at approximately this stage there is an increase in the total number of pulmonary vessels and vasomotor activity, reflecting the developing pulmonary vasculature during the late canalicular phase of lung development.[8] Fetal breathing activity also becomes more regular.[9] Each subject was included in the study once. One woman had a twin gestation. Mean maternal age was 28.3 years (range, 18 to 42 years); maternal parity ranged from 0 to 5. No medications were prescribed. On ultrasonographic examination there was a normal amount of amniotic fluid. Measurements of the fetal biparietal diameter, upper abdominal and head circumference, and femur length revealed a normal-sized fetus without gross structural anomalies.

The second group consisted of 32 women who were admitted during the study period either from our own outpatient clinic or were referred from other centers because of premature rupture of membranes before 28 weeks' gestation. Mean gestational age was 22.9 weeks (range, 16 to 27 weeks). Fetal ductal flow velocity measurements were begun at 25 weeks' gestation. Premature rupture of membranes must have resulted in severe oligohydramnios and had to be present over a period of 3 weeks or more before delivery. Severe oligohydramnios was defined as the absence of an amniotic fluid pool of more than 1 cm, measured in two planes on ultrasound examination. Mean maternal age in this group was 27.9 years (range, 22 to 35 years); maternal parity varied from 0 to 4. Fetal biparietal diameter, upper abdominal, and head circumference revealed a normal-sized fetus without gross structural defects. In all women with premature rupture of membranes, tocolysis was established by intravenous administration of fenoterol. No corticosteroids were prescribed, and only cases with no signs of amnionitis were studied.

Fetal ductal flow velocity measurements were performed with a combined two-dimensional real-time and continuous-wave Doppler system (Diasonics CV 400). A 3.0 MHz transducer was used. The sector scanner operated at power outputs <100 mW/cm^2 in both imaging and Doppler modes by manufacturer's specifications. All women were studied while in the semirecumbent position. A longitudinal cross-section of the fetal ductus arteriosus was obtained on a short-axis view of the fetal heart parallel to the fetal spine as first described by Huhta et al.[7] The aortic arch was distinguished from the ductal arch by visualization of the carotid arteries. The cursor line was placed in the ductus near the junction of the ductus and the descending aorta. The angle of insonation was maintained below 5 degrees. On the same short-axis view, movements of the fetal thoracic wall and diaphragm reflecting breathing movements can be observed, while the Doppler flow velocity measurements in the ductus arteriosus are performed parallel to the ductal flow direction without changing the position of the transducer.

Fetal breathing activity was defined as periodic inward movements of the fetal chest wall with downward movements of the fetal diaphragm. Continuous fetal breathing was considered present when the interval between two consecutive breathing movements was <6 seconds. In the normal developing fetus, the second trimester is characterized by irregular and sporadic breathing movements. With advancing gestational age fetal breathing becomes more regular with a reduction in breathing rate,[9] whereas the percentage of time spent breathing does not differ significantly under fasting conditions.[10, 11] Fetal breathing activity is stimulated by glucose loading.[12] This breathing response increases with advancing gestational age.[13] For this reason and to obtain accurate timing of breathing-related Doppler flow measurements, it was decided to stimulate fetal breathing activity by maternal glucose administration at the onset of each study period, after normal carbohydrate metabolism had been established (postprandial capillary glucose level <7 mmol/L) and after intrauterine growth retardation had been ruled out. Assuming that the severely growth-retarded fetus is chronically hypoxemic, a sudden surge in glucose might lead to the development of metabolic acidosis and result in fetal death.[14]

In the group of patients with prolonged severe oligohydramnios, 250 ml of a 10% glucose solution (27.5 gm) was given intravenously over a period of 15 minutes. All patients already had an intravenous line in place. In cases of prolonged severe oligohydramnios the percentage of time spent breathing is not markedly altered,[15] or is even increased.[16] In the women with normal pregnancies a single dose of 50 gm of glucose was administered orally. Peak maternal glucose levels are reached approximately 10 minutes after intravenous glucose loading and approximately 60 minutes after oral glucose loading.[13] Both routes result in a comparable rise in maternal plasma glucose concentration; moreover, the incidence and fetal breathing rate are not affected differently after oral or intravenous glucose administration.[13] We therefore did not consider it ethically appropriate to use the intravenous route in the normal group. Doppler flow velocity waveform recordings in the fetal ductus arteriosus were started at the time of the expected increase in fetal breathing activity, 30 minutes after intravenous glucose adminis-

tration[15] and 2 hours after oral glucose administration[13] to the mother. The time delay between the peak of the maternal capillary glucose level and increase in fetal breathing incidence may be explained by the local excess of carbon dioxide produced by increased oxidation of glucose, stimulating the chemosensitive areas of the brain stem.[17, 18]

Maximum flow velocity waveforms were obtained over a 15-second period after a period of continuous fetal breathing activity was observed. To ensure the presence of fetal breathing activity throughout the Doppler flow velocity recording, fetal breathing movements had to still be present after completion of the recording. The blood flow velocity waveforms were recorded on videotape and approximately 30 consecutive waveforms were obtained from hard copies of each measurement. With a microcomputer (Olivetti M24, Ivrea, Italy), the difference in peak systolic velocity between two flow velocity waveforms representing the expiratory and inspiratory phase of the fetal breathing movement was calculated. The mean difference in ductal peak systolic flow velocity modulation was established from the total number of waveform recordings during breathing activity. The diastolic portion of the ductal flow velocity waveform was not evaluated because it bears no direct relationship with shunting of blood from the pulmonary artery through the ductus. All Doppler measurements were performed by one observer (K. v. d. M.). Information on fetal ductal flow velocity recordings was not made available to the clinician responsible for the obstetric management.

The diagnosis of pulmonary hypoplasia was based on a reduced lung/body weight ratio[19] (ratio <0.015 for gestational ages <28 weeks or <0.012 for gestational ages ≥ 28 weeks) established at autopsy or on combined clinical finding of (1) immediate onset of severe respiratory insufficiency after birth requiring high-pressure artificial ventilation; (2) chest radiographs demonstrating small lung volume, with the diaphragm elevated above the seventh rib, downward sloping ribs, and a bell-shaped thoracic cage; (3) clinical respiratory disease that did not conform to the classical model of hyaline membrane disease.

The number of blood flow velocity waveforms studied in the fetal ductus arteriosus in normal pregnancy is expressed as mean ± 1 SD. A scattergram for mean ductal peak systolic flow velocity modulation in relation to gestational age was developed for all women without oligohydramnios. From the data collected in normal pregnancy, the regression line as well as the 1st, 5th, 95th, and 99th percentile lines were estimated from linear regression analysis after logarithmic transformation of ductal blood flow velocity modulation. For the estimation of the regression lines it was assumed that the residual term displays a normal distribution with the mean of zero.

Results

Normal pregnancy. Poor-quality fetal ductal flow velocity signals were obtained in six of 55 normal pregnancies because of excessive fetal body movements, lateral position of the fetal spine, or technical failure of the video equipment. In the remaining 49 pregnancies (50 fetuses), a technically acceptable recording during fetal breathing activity was documented. Oral glucose loading was performed in each instance. Mean maternal capillary glucose level was 6.4 ± 1.3 mmol/L, measured 1 hour after oral glucose administration. Fetal birth weight was between the 10th and 90th percentile for gestational age[20] corrected for maternal parity and fetal sex. Neonatal lung performance was normal. The mean number of blood flow velocity waveforms studied in the fetal ductus arteriosus was 18.1 ± 6.8.

Modulation of the ductal flow velocity waveform was characterized by a momentary reduction of peak systolic velocity during the inspiration phase (Fig. 1). Regression analysis of the ductal blood flow velocity modulation data obtained from the 50 normally developing fetuses (open circles, Fig. 2) revealed an exponential increase in ductal blood flow velocity modulation with advancing gestational age; the regression equation was $\ln \Delta PV = 0.537 + 0.076 \times$ weeks with $R^2 = 0.90$, $p < 0.0001$, where ΔPV equals ductal blood flow velocity modulation. The regression equations for the 99th and 1st percentile lines were: $0.537 + 0.076 \times$ weeks $\pm 2.58 \times 0.1017$, and for the 95th and 5th percentile lines: $0.537 + 0.076 \times$ weeks $\pm 1.96 \times 0.1017$, in which 0.1017 equals the estimated standard deviation of the residual term and 2.58 and 1.96 represent the respective two-tailed 1% and 5% points of the standard normal distribution. Fig. 2 presents the regression line and the estimated four percentile lines after transformation of the variable ln ΔPV back to its normal level by using the antilog.

Prolonged severe oligohydramnios. Of the 32 women who were admitted to our hospital during the study period because of premature rupture of membranes before 28 weeks' gestation, nine were not included in the study because no severe oligohydramnios developed. Six women were removed from the study because amnionitis developed and the women were delivered within 1 week after premature rupture of membranes; three other women were delivered before 25 weeks' gestational age. One woman was removed from the study because of intrauterine growth retardation and preeclampsia necessitating use of antihypertensive drugs; thus 13 women remained for further analysis. In these 13 women mean gestational age at onset of oligohydramnios was 23.3 ± 4.1 weeks (1 SD) and mean duration of oligohydramnios was 6.8 ± 2.9 weeks (1 SD). The maximum time interval between the last Doppler flow recording and delivery was 7 days.

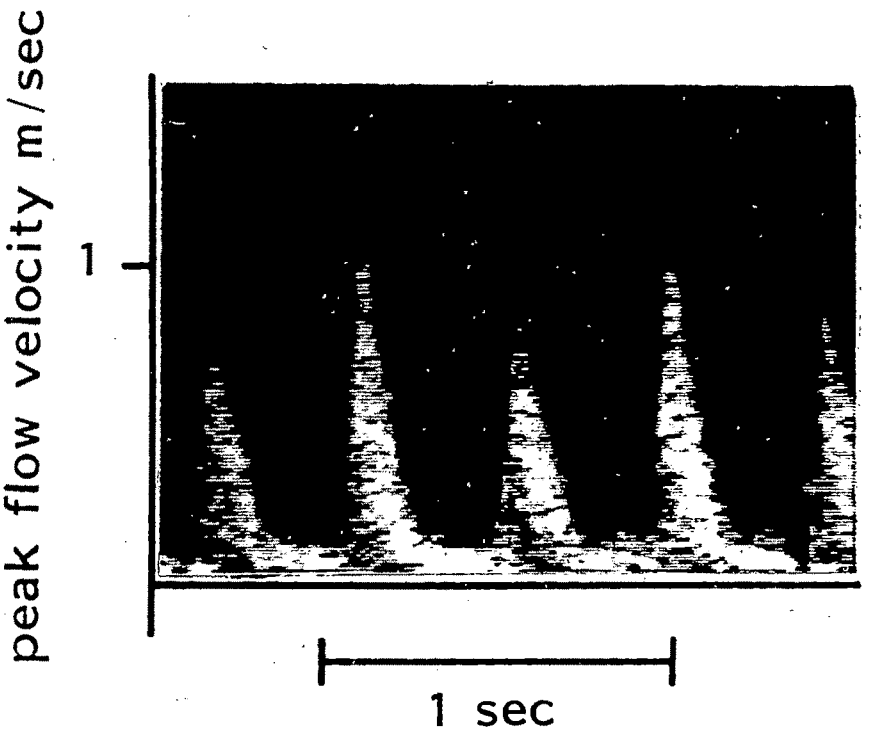


Fig. 1. Blood flow velocity waveforms obtained from the fetal ductus arteriosus during fetal breathing activity.

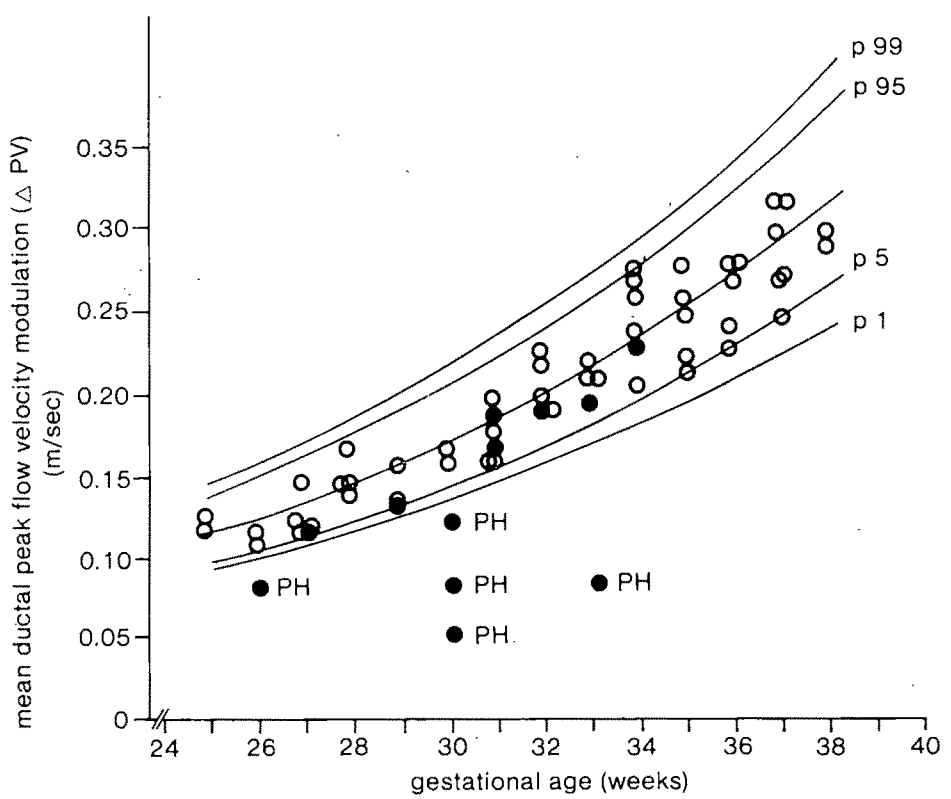


Fig. 2. Mean breathing-related ductal peak systolic flow velocity modulation relative to gestational age for 49 normal pregnancies (50 fetuses, *open circles*) with the estimated 1st, 5th, 95th, and 99th percentile lines and last ductal blood flow velocity modulation value before delivery of 12 cases with prolonged severe oligohydramnios as a result of ruptured membranes *(closed circles). PH,* Pulmonary hypoplasia.

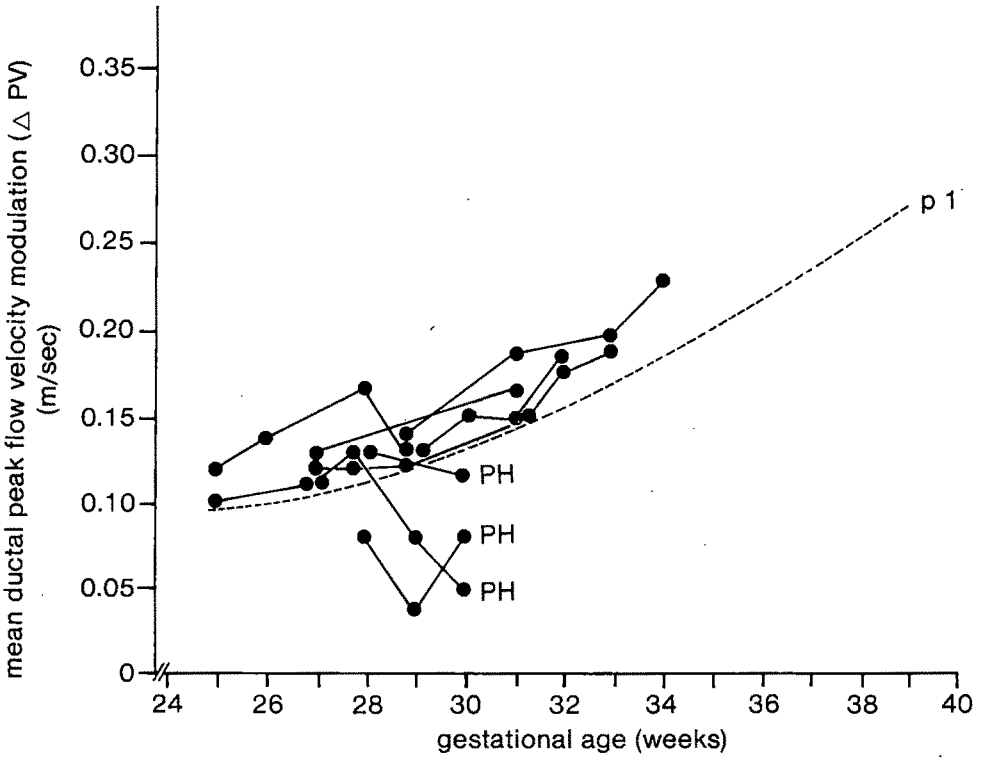


Fig. 3. The first percentile line of the normal population *(dotted line)* and the mean breathing-related ductal peak systolic flow velocity modulation relative to gestational age for nine cases of prolonged severe oligohydramnios as a result of ruptured membranes *(closed circles)* in which serial recordings were obtained. *PH,* Pulmonary hypoplasia.

Mean maternal capillary glucose level measured 10 minutes after intravenous glucose administration was 6.2 ± 2.5 mmol/L. Fetal birth weight was between the 10th and 90th percentile for gestational age,[20] corrected for maternal parity and fetal sex. Fetal heart rate always varied between 120 and 160 beats/min. Forty-one fetal ductal flow velocity recordings were technically acceptable for further analysis. Prenatal findings and fetal outcome are presented in Tables IA, IB, and II. The mean number of blood flow velocity waveforms studied in this group was 16.7 ± 7.6. Seven recordings were obtained in the absence of fetal breathing activity. In patient no. 1, absence of fetal breathing activity was documented on three different occasions despite maternal intravenous glucose administration; neonatal lung performance was normal. In patient no. 3, no fetal breathing activity could be documented in three recordings. These recordings were not preceded by intravenous glucose administration because glucose metabolism became abnormal after the first Doppler recording. Neonatal lung performance was normal in this case. Despite intravenous glucose administration we were unable to document fetal breathing activity in patient no. 9 in one of five occasions. Thirty-four recordings were obtained during fetal breathing activity (patients 2 through 13). Longitudinal follow-up was feasible in nine of 13 women with oligohydramnios and accounted for 31 ductal blood flow velocity modulation measurements (Fig. 3; closed circles). In the remaining three women only one recording was obtained. When the ductal blood flow velocity modulation data nearest to delivery were considered (mean, 3.8 days; range, 0 to 7 days; Fig. 2, closed circles), five women had ductal blood flow velocity modulation values below the 1st percentile of the reference curve. These reduced values were associated with pulmonary hypoplasia. For the remaining seven women ductal blood flow velocity modulation values were within the normal range of the reference curve and were associated with normal neonatal lung performance. For the group of women with prolonged severe oligohydramnios that resulted in pulmonary hypoplasia, the mean gestational age at the onset of oligohydramnios was 21.8 ± 4.6 weeks (1 SD) and the mean duration of oligohydramnios was 8.6 ± 2.9 weeks (1 SD). For the group of women with prolonged severe oligohydramnios with normal neonatal lung performance, the mean gestational age at the onset of oligohydramnios was 24.3 ± 3.7 weeks (1 SD) and the mean duration of oligohydramnios was 7.0 ± 2.5 weeks (1 SD). Four of five cases of pulmonary hypoplasia were confirmed at autopsy. In the remaining in-

Table IA. Prenatal findings of group with prolonged severe oligohydramnios resulting in normal neonatal lung performance

Patient No.	Gestational age (wk)			Maternal glucose loading (intravenous)	Fetal breathing movements	ΔPV (m/sec)
	At onset of oligohydramnios	At Doppler measurement	At delivery			
1	26	27	30	+	†	‡
		28		+	†	‡
		29		+	†	‡
3	27	27	32	+	+	0.13
		29		*	†	‡
		30		*	†	‡
		31		*	+	0.17
		32		*	†	‡
7	24	25	29	+	+	0.12
		26		+	+	0.14
		28		+	+	0.17
		29		+	+	0.13
8	26	29	32	+	+	0.13
		30		+	+	0.16
		31		+	+	0.15
		32		+	+	0.19
9	27	29	35	+	+	0.13
		30		+	†	‡
		31		+	+	0.19
		33		+	+	0.20
		34		+	+	0.23
10	22	31	32	+	+	0.19
12	26	27	33	+	+	0.12
		28		+	+	0.12
		29		+	+	0.12
		31		+	+	0.15
		32		+	+	0.18
		33		+	+	0.19
13	16	25	27	+	+	0.10
		27		+	+	0.11

ΔPV, Mean ductal peak systolic flow velocity modulation.

*There was no administration of glucose to the mother.

†No fetal breathing movements could be observed during that measurement.

‡There were no ductal peak flow velocity modulations observed, which is logical since in these cases no fetal breathing movements could be documented.

fant the diagnosis of pulmonary hypoplasia was based on the aforementioned clinical criteria. This infant was treated with 2 months of high-pressure artificial ventilation and now suffers from bronchopulmonary dysplasia and severe brain damage caused by prolonged hypoxia after bilateral pneumothorax. The longitudinal ductal blood flow velocity modulation data (Fig. 3) revealed that two of three fetuses in which pulmonary hypoplasia eventually developed demonstrated a downward trend in ductal blood flow velocity modulation, resulting in values below the 1st percentile of the reference curve.

Comment

Our data demonstrate that during normal pregnancy blood flow velocity waveforms obtained from the fetal ductus arteriosus are modulated by fetal breathing movements. During the inspiration phase of the fetal breathing cycle there is a momentary reduction of ductal systolic peak flow velocity. Because of limitations in the lateral resolution of current ultrasonographic equipment, no accurate measurements of ductal diameter could be obtained. Because dilatation of the fetal ductus arteriosus beyond its resting dimension has not been observed, and agents have not been identified that are capable of such dilatation, it seems unlikely that the reduction in ductal peak systolic flow velocity during fetal breathing activity is caused by increasing ductal diameter.[21] For this reason it is also unlikely that the blood flow velocity changes are caused directly by pressure changes in the fetal chest and abdomen during fetal breathing activity. The observed reduction in ductal peak systolic flow velocity during fetal breathing activity is in agreement with fetal lamb experiments in which it was established that total pulmonary vascular resistance decreased during lung expansion.[4] The subsequent increased perfusion of the pulmonary vascular bed was demonstrated by a rise in pulmonary artery flow and decrease in ductal flow, reflecting reduced right to left shunting. Fetal lamb studies have also

Table IB. Prenatal findings of group with prolonged severe oligohydramnios resulting in pulmonary hypoplasia

Patient No.	Gestational age (wk)			Maternal glucose loading (intravenous)	Fetal breathing movements	ΔPV (m/sec)
	At onset of oligohydramnios	At Doppler measurement	At delivery			
2	25	28	31	+	+	0.08*
		29		+	+	0.04*
		30		+	+	0.08*
4	17	27	30	+	+	0.11
		28		+	+	0.13
		29		+	+	0.08*
		30		+	+	0.05*
5	23	28	30	+	+	0.13
		30		+	+	0.12*
6	27	33	34	+	+	0.08*
11	17	26	27	+	+	0.08*

ΔPV, Mean ductal peak systolic flow velocity modulation.
*Below 1st percentile.

Table II. Fetal outcome of group with prolonged severe oligohydramnios

Patient No.	Fetal outcome	Pulmonary hypoplasia		
		Clinical evidence	Confirmed at autopsy	Lung/body weight ratio
1	Uneventful	–	–	–
2	Died immediately post partum	+	+	0.009
3	Uneventful	–	–	–
4	Died immediately post partum	+	+	0.012
5	Died 4 hr post partum	+	+	0.005
6	2 mo of artificial ventilation, bronchopulmonary dysplasia, brain damage	+	–	–
7	Uneventful	–	–	–
8	Uneventful	–	–	–
9	Uneventful	–	–	–
10	Uneventful	–	–	–
11	Died immediately post partum	+	+	0.013
12	Uneventful	–	–	–
13	Uneventful	–	–	–

shown that there is a rise in pulmonary blood flow and reduction in pulmonary vascular resistance with advancing gestational age caused by an increase in the total number of pulmonary vessels and increased vasomotor activity.[5] In the human fetus this phenomenon begins during the late canalicular phase (±23 through ±26 weeks) and continues during the saccular and alveolar phase of lung development (±26 through ±40 weeks).[8, 22] This may explain the small modulations in ductal peak systolic flow velocity at 25 weeks and subsequent exponential rise during the third trimester of pregnancy.

In the presence of oligohydramnios lung development may be arrested in the canalicular phase,[23] resulting in reduced lung volume and impaired development of the vascular bed, which is associated with a fixed high pulmonary vascular resistance.[6, 22, 24] This may explain the reduced ductal peak systolic flow velocity modulation observed by us in the fetuses with pulmonary hypoplasia. The predictive value of normal ductal peak systolic flow velocity modulation for continuing lung growth was 100%, as was the predictive value of reduced modulation for pulmonary hypoplasia. Various clinical tests have been suggested with regard to the antepartum diagnosis of developing pulmonary hypoplasia. A close association has been reported between a low fetal thoracic circumference or low thoracic circumference/abdominal circumference ratio and poor neonatal lung performance.[25-27] Both parameters are useful but late indicators of pulmonary hypoplasia. If it is assumed that breathing-related ductal peak systolic flow velocity modulation and pulmonary vascular resistance are inversely related, then the longitudinal data in our study suggest that serial recording of ductal peak systolic flow velocity modulation during breathing activity may be helpful in assessing

the progression of abnormal lung development. Such assessment would allow a more optimal obstetric management in cases of prolonged severe oligohydramnios as a result of ruptured membranes at a stage of pregnancy when extrauterine survival can be expected. A larger longitudinal study is needed to substantiate this premise. The secondary rise in breathing-related ductal peak systolic flow velocity modulation in one case (Fig. 3) may be the result of the administration of 100 mg of indomethacin to the mother shortly before the Doppler flow velocity recording. It has recently been demonstrated that use of the prostaglandin synthetase inhibitor indomethacin may lead to ductal constriction as determined by a significant rise in ductal peak systolic and end-diastolic velocities. In our case mean peak systolic velocity rose from 1.10 to 1.60 m/sec. The subsequent increase in breathing-related ductal peak systolic flow velocity modulation was determined by a more pronounced peak systolic rise during expiration compared with inspiration. Because the constrictive effect of indomethacin may be observed as long as 12 hours after drug administration, studies of ductal flow modulation should be conducted beyond this period.[7, 28] In our study administration of fenoterol was not considered to affect ductal peak systolic flow velocity because the fetal heart rate was within the physiologic range, during which no fetal heart rate dependency of ductal peak systolic flow velocity had been documented.[29] Fetal breathing activity itself has been reported to be helpful in assessment of fetal lung development in cases of prolonged severe oligohydramnios. Fetal breathing movements are important for facilitating lung growth. It has been shown that upper cervical cord injury in rabbit fetuses at 28 to 29 days' gestation results in a reduction in lung weight and total deoxyribonucleic acid content, and injury before 24 days results in retarded maturation. These effects were explained by cessation of fetal breathing activity.[30] Although Blott et al.[2] suggested that the absence of fetal breathing movement is highly predictive for pulmonary hypoplasia, this finding was challenged by Moessinger et al.[3] who stated that observation of fetal breathing activity is not helpful in identifying patients with oligohydramnios at risk of pulmonary hypoplasia. Results of our study support the latter statement. We were unable to observe fetal breathing activity on three occasions in one patient (Table IA) despite maternal intravenous glucose loading; neonatal lung performance was normal. Conversely, fetal breathing movements were established in five fetuses with pulmonary hypoplasia after birth (Table IB).

We conclude that fetal ductal peak systolic flow velocity is modulated by fetal breathing activity in normal late second- and third-trimester pregnancies. This ductal flow modulation exhibits an exponentional increase with advancing gestational age, suggesting the developing pulmonary vascular bed. In cases of prolonged severe oligohydramnios caused by ruptured membranes, normal ductal flow modulation is associated with normal neonatal lung performance, whereas pulmonary hypoplasia was established in cases of reduced ductal flow modulation.

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Prenatal diagnosis of a chest wall mass with ultrasonography and Doppler velocimetry

A case report

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An isolated mass protruding from the chest wall of the fetus was visualized by ultrasonography. Doppler velocimetry over the mass revealed low-resistance blood flow through cystic areas, implicating a highly vascular lesion. An operative delivery was performed to avoid possible rupture of the mass. (Am J Obstet Gynecol 1990;163:567-9.)

Key words: Hemangioma, Doppler velocimetry, prenatal diagnosis

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Internal chest tumors have been diagnosed prenatally in numerous cases. However, an external chest wall mass has not been visualized in utero by ultrasonography to our knowledge. An understanding of external tumors located in other anatomic regions of the fetus and application of Doppler velocimetry were helpful in the management of this case.

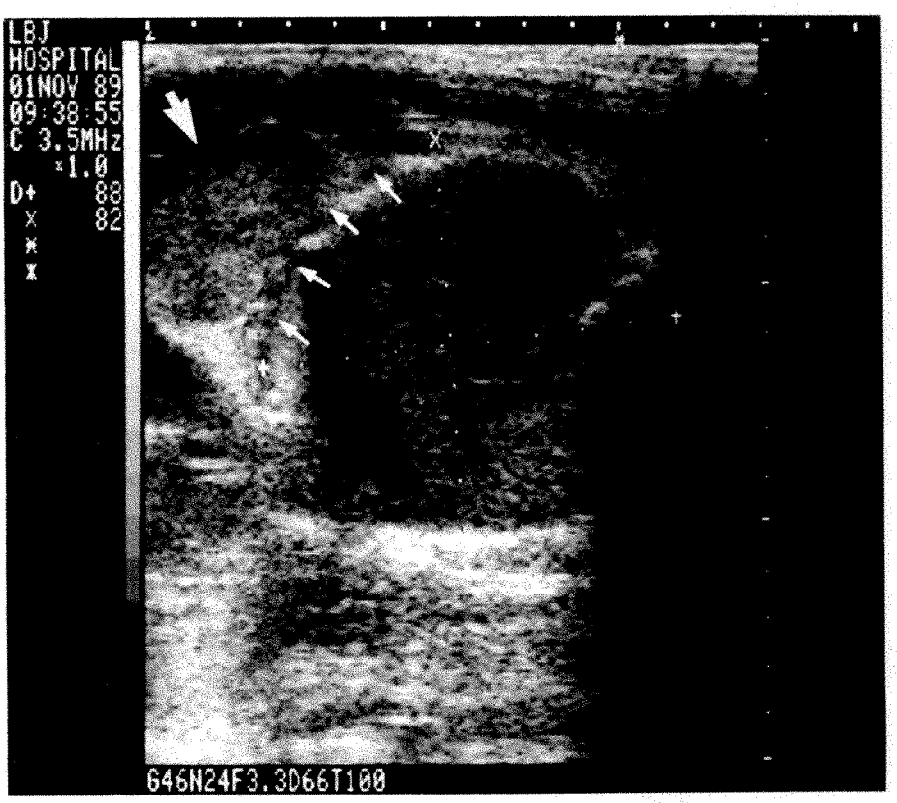


Fig. 1. Ultrasonography of chest circumference. *Small arrows* show outline of chest wall. *Large arrow* demonstrates mass.



Fig. 2. Cavernous hemangioma on infant's chest wall.

Case report

A 17-year-old black primigravid patient was referred to our tertiary care center for an abnormal screening ultrasonogram. Her prenatal course had been unremarkable, including a normal maternal serum α-fetoprotein at 16 weeks' gestation. Her medical history was not significant for any diseases including dermatologic or vascular disorders. The patient denied any use of medications or exposure to drugs during the pregnancy. Her family history disclosed no neural tube defects, mental retardation, or birth defects. The father of the fetus had a history of a right chest wall mass seen at birth and removed at age 6. The pathologic diagnosis was mature teratoma.

Sequential ultrasonography with General Electric model 3000 equipment showed a normal-appearing male fetus except for a discrete right-sided anterior chest wall mass, that did not involve the axilla or neck. Free movement of the upper extremities was noted. The contents within the chest appeared normal, including a four-chamber heart. The mass projected from the external chest and did not appear to penetrate the ribs. It measured 3.4 × 3.1 cm and was echodense with three small (0.3 cm) hypoechoic structures within the tumor. We performed continuous Doppler velocimetry over the mass with a 3.5 MHz transducer. A flow wave pattern with a systolic/diastolic ratio of 1.5 was noted, consistent with blood flow through low resistance channels.[1] Serial ultrasonography with a General Electric model 3200 showed little growth of the mass over the next eight weeks. Fig. 1 shows the mass on real-time ultrasonography.

At 35 weeks' gestation the patient came to the labor and delivery suite with a chief complaint of leakage of fluid per vagina for 6 hours and contractions every 3 minutes. Vaginal examination showed the cervix to be 4 cm dilated and completely effaced with a cephalic presentation. A male infant weighing 2680 gm with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, was delivered by low transverse cesarean section. A purple, spongy mass was noted on the right anterior chest wall that displaced the areola laterally (Fig. 2). The mass then measured 4.3 × 4.2 cm. No bruits were heard or pulsations felt within the mass. The infant's platelet count was 175,000/cm^3. On the fifth day of life, the infant had the mass resected without difficulty. The histologic diagnosis was cavernous hemangioma. The infant was discharged on the second postoperative day.

At 6 months of age the infant was healthy and doing well.

Comment

The appearance of a solid and cystic mass by ultrasonography elsewhere on the outer surface of the fetus led to a differential diagnosis including teratoma, hemangioma, and mesenchymal sarcoma. With the use of Doppler velocimetry, we demonstrated that the mass had a low-resistance blood flow. Similar results were obtained in a case of a craniofacial hemangioma.[1] We speculate that low vascular resistance as evaluated by Doppler ultrasonography could differentiate vascular lesions such as hemangiomas from neoplasias such as teratomas. However, further Doppler studies of fetal tumors are necessary to substantiate the potential of this diagnostic modality.

The size of the mass did not suggest that soft tissue dystocia was likely. However, a cesarean section was performed because the risk of trauma to a very vascular mass lesion existed. Hemangiomas in the newborn have been noted to have a microangiopathic anemia and thrombocytopenia caused by trauma of the blood elements as flow occurs through the vascular lesion.[2] Therefore abdominal delivery may be appropriate in the management of rare external masses of the fetus.

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Relationship of fetal biophysical profile and blood gas values at cordocentesis in severely growth-retarded fetuses

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In 14 severely growth-retarded fetuses the biophysical profile score was analyzed in relation to blood Po_2, pH, oxygen saturation, and oxygen content in samples obtained by cordocentesis. The data suggest that the biophysical profile score can predict the degree of fetal acidemia. (Am J Obstet Gynecol 1990;163:569-71.)

Key words: Biophysical profile, cordocentesis, fetal blood gases, intrauterine growth retardation

The biophysical profile is widely used for the assessment of fetal well-being. All previous studies with the biophysical profile have related the results of the test with outcome of pregnancy or with cord blood gas levels at delivery.[1, 2] This study examines the relationship between the biophysical profile and fetal blood gas levels in samples obtained by cordocentesis.

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Patients and methods

In 14 severely growth-retarded fetuses that were referred to our unit for further assessment at 25 to 39 weeks' gestation, the biophysical profile was studied immediately before umbilical venous blood sampling. The methods and definitions for fetal tone, fetal gross body movements, fetal breathing movements, amniotic fluid volume, and fetal heart rate reactivity were those described by Manning.[1] Cordocentesis was performed without maternal sedation or fetal paralysis. All fetuses were anatomically and chromosomally normal. The fetal blood gas and hemoglobin levels (grams per deciliter) were measured by Radiometer ABL 330 (Copen-

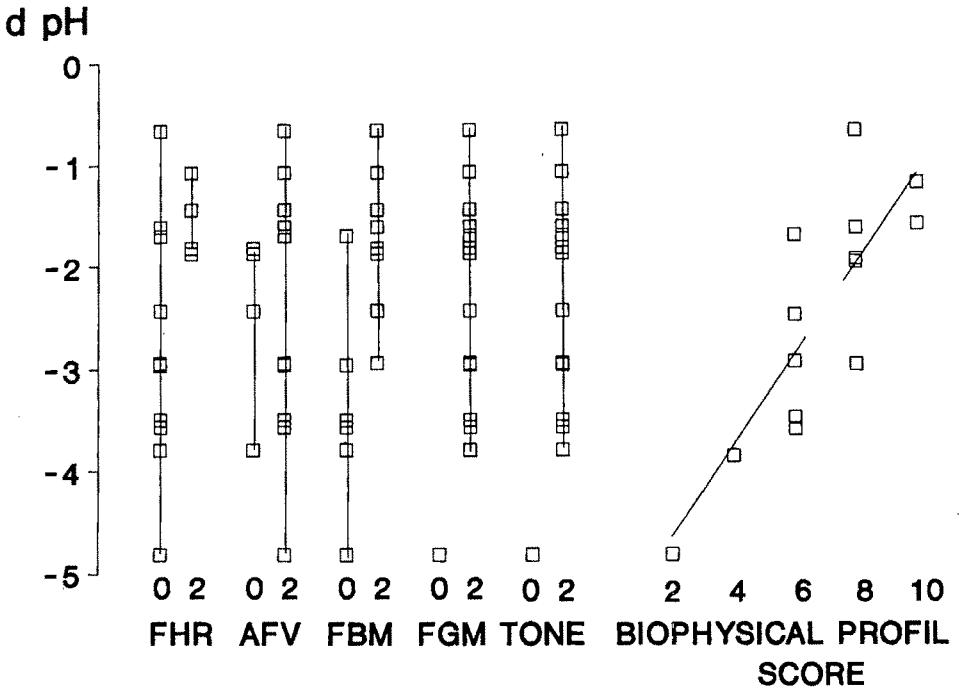


Fig. 1. Relation of umbilical venous acidemia (change in pH in SDs from normal mean for gestation) and fetal heart rate *(FHR)* pattern, amniotic fluid volume *(AFV)*, fetal breathing movements *(FBM)*, fetal gross body movements *(FGM)*, fetal tone *(left)*, and total biophysical profile score *(right;* $r = 0.812$, $p < 0.001$) in 14 severely growth-retarded fetuses.

Table I. Umbilical venous blood sample data, biophysical profile, and outcome of 14 severely growth-retarded fetuses

	Umbilical venous blood data							*Biophysical profile*					*Outcome*		
Case no.	*GA (wk)*	Po_2 *(mm Hg)*	Pco_2 *(mm Hg)*	*pH*	*Sat (%)*	*Hb (gm/L)*	O_2c *(mmol/L)*	*AFV*	*Tone*	*FGM*	*FBM*	*FHR*	*Outcome*	*Wk*	*Gm*
1	25	17.3	42.7	7.34	41	12.6	3.097	2	2	2	0	0	LB	29	580
2	27	23.8	50.3	7.32	64	10.3	3.967	2	2	2	0	0	IUD	34	600
3	28	24.7	38.2	7.40	62	15.8	5.809	2	2	2	2	0	NND	30	800
4	28	28.3	34.6	7.37	72	7.8	3.350	2	2	2	0	0	NND	29	880
5	29	28.0	44.6	7.37	71	12.4	5.281	2	2	2	2	0	LB	30	630
6	29	36.5	44.7	7.28	87	9.5	4.952	2	0	0	0	0	LB	30	950
7	30	27.4	41.4	7.33	72	7.7	0.332	2	2	2	2	0	LB	30	1015
8	30	21.0	39.5	7.31	57	12.3	4.171	2	2	2	0	0	LB	30	836
9	32	30.7	38.6	7.34	78	12.7	5.908	0	2	2	2	0	LB	33	1330
10	32	22.8	41.5	7.35	59	14.8	5.242	0	2	2	2	2	LB	32	1020
11	33	8.1	52.6	7.30	9	14.2	0.734	0	2	2	0	0	LB	33	1330
12	36	26.9	45.2	7.37	69	13.2	5.446	2	2	2	2	2	LB	37	1840
13	37	25.6	45.9	7.35	67	15.7	6.269	2	2	2	2	2	LB	37	1463
14	39	28.5	42.6	7.34	74	18.5	8.185	0	2	2	2	2	LB	39	1540

GA, Gestational age in completed weeks; *Sat*, saturation; *Hb*, hemoglobin; O_2c, oxygen content; *AVF*, amniotic fluid volume; *FGM*, fetal gross body movements; *FBM*, fetal breathing movements; *FHR*, fetal heart rate pattern; *LB*, live birth; *IUD*, intrauterine death; *NND*, neonatal death.

hagen, Denmark) and Coulter S-plus counter (Coulter Electronics, Luton, England), respectively. The oxygen saturation and oxygen content were calculated. The individual values of the growth-retarded fetuses were subtracted from the appropriate mean for gestation of our reference ranges and expressed as Δ values in SDs [normal ranges: $Po_2 = 62.3 - 0.81 \times$ weeks (mm Hg), SD = 7.51, $n = 268$; $Pco_2 = 28.1 + 0.25 \times$ weeks (mm Hg), SD = 3.23, $n = 268$; pH = $7.47 - 0.002 \times$ weeks, SD = 0.03, $n = 268$; oxygen saturation = $1.013 - 0.007 \times$ weeks (%), SD = 0.06, $n = 268$; hemoglobin = $7.6 + 0.18 \times$ weeks (gm/L),

SD = 1.2, n = 555; oxygen content = 5.36 + 0.03 × weeks (mmol/L), SD = 0.73, n = 194].

Results

Fetal blood sampling data, the biophysical profile score, and pregnancy outcome are given in Table I. The biophysical profile score was significantly correlated to Δ pH (n = 14, r = 0.840, $p < 0.001$; Fig. 1) but not to Δ Po_2 (r = 0.25), Δ Pco_2 (r = −0.25), Δ oxygen saturation (r = 0.25), Δ hemoglobin (r = 0.34), or Δ oxygen content (r = 0.48). Although the indices of oxygenation (Po_2, oxygen saturation, oxygen content) were lower in the group of fetuses with nonreactive fetal heart rate or absent fetal breathing movement than in the group with reactive fetal heart rate and the presence of fetal breathing movement, the differences were not statistically significant.

Comment

This preliminary study in a group of highly compromised growth-retarded fetuses suggests that the biophysical profile score can predict the degree of fetal acidemia and confirms the findings of Vintzileos et al.[2] that fetal heart rate reactivity and fetal breathing movements are the first, whereas fetal gross body movement and tone are the last biophysical activities to be compromised during acidemia. If the aim of antenatal testing is to diagnose fetal acidemia, more useful information is obtained from the sequential examination of the individual components of the biophysical profile score than the total score. A reactive fetal heart rate was always associated with a pH above the 2.5th percentile. A nonreactive fetal heart rate can be investigated further by sonography for the diagnosis of oligohydramnios, which was always associated fetal acidemia. However, absence of oligohydramnios, certainly for fetuses of <32 weeks' gestation, does not exclude acidemia. Subsequent sonographic examination for fetal tone and activity will help distinguish between acidemic and nonacidemic fetuses in the majority of cases; indeed, absence of tone and fetal gross body movements may identify a subgroup of severely acidemic fetuses. Further improvement of the biophysical profile score may be obtained by quantification of the incidence of movements and use of a fetal heart rate classification that takes into account the gestational effect on reactivity.

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Successful treatment of postpartum shock caused by amniotic fluid embolism with cardiopulmonary bypass and pulmonary artery thromboembolectomy

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We report the successful treatment of a moribund patient as a result of amniotic fluid embolism with cardiopulmonary bypass and open pulmonary artery thromboembolectomy. Review of the literature indicates that this is the first reported case of treatment of amniotic fluid embolism with cardiopulmonary bypass and pulmonary thromboembolectomy. (Am J Obstet Gynecol 1990;163:572-4.)

Key words: Amniotic fluid embolism, postpartum shock, disseminated intravascular coagulation

Amniotic fluid embolism is a highly lethal disorder that complicates an estimated 1 in 30,000 pregnancies. Despite its rarity it remains the most common cause of death in labor, during pregnancy, and in the immediate postpartum period. The breakdown of the maternal-fetal barrier with the release of fetal particulate matter into the maternal circulation is responsible for the clinical manifestations of this disorder, which include cardiovascular collapse, pulmonary arterial thrombosis, and severe coagulopathy. Because there has been no specific therapy for this disorder, treatment has traditionally been supportive and involves the maintenance of blood volume, pharmacologic support of the circulation, administration of oxygen, and attempted reversal of the coagulopathy with blood components. Despite these efforts the outcome has remained dismal with an overall expected mortality of 86%.[1] Theoretically, an attempt at surgical removal of the fetal products of gestation and thrombus from the maternal pulmonary circulation should be advantageous in restoration of normal physiologic characteristics. This approach was first suggested by Altcheck and Litwak[2] in 1966, but to our knowledge has not been used clinically until this report.

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6/1/20495

Case report

A 29-year-old woman, gravida 4, para 4, was air evacuated to Bellevue Hospital on Nov. 12, 1988, for the treatment of postpartum shock. Earlier that day the patient had undergone an uncomplicated cesarean section of a 40-week gestation with the delivery of a normal female infant. One hour postpartum the patient sustained a sudden cardiopulmonary arrest. She was resuscitated with closed cardiac massage and assisted ventilation. Marginal blood pressure was maintained with a large dose of inotropic drugs. The diagnosis of pulmonary embolism was suspected as a result of significant arterial desaturation. A pulmonary perfusion scan demonstrated massive embolism to the left lung (Fig. 1, *A*).

The patient was transferred to Bellevue Hospital for possible surgical thrombectomy. On arrival the systolic blood pressure was 80 mm Hg with the patient receiving 30 μg/min/kg dopamine infusion. Arterial blood gas determination demonstrated severe desaturation (Po_2 of 80 torr with complete assisted ventilation; Fio_2, 1.00). In addition, there was external evidence of severe ongoing coagulopathy with bleeding from all intravenous puncture sites, the vagina, and the abdominal incision. Because the patient was too unstable for further workup, she was taken directly to the operating room.

The heart was exposed through a median sternotomy incision. The most striking finding was a distended right ventricle that was contracting poorly. After full heparinization, cardiopulmonary bypass was instituted at a flow rate of 2 L/min/m² at a temperature of 32° C. Cardioplegic arrest was obtained with cold blood potassium cardioplegia; continuous topical hypothermia was maintained with cooled saline solution.

The pulmonary artery was then opened axially starting at the main pulmonary artery and directed onto



Fig. 1. Pulmonary perfusion scans: preoperative **(a)**, 2 weeks after operation **(b)**, and 3 months after operation **(c)**.

the left pulmonary artery. A large amount of friable thrombus was removed, most of which formed a cast of the pulmonary arterial tree. Subsequent microscopic examination of this material demonstrated a high concentration of fetal squamous cells, confirming the diagnosis of amniotic fluid embolism. The incision was then closed with a running 5-0 Prolene suture (Ethicon, Inc., Somerville, N.J.).

The patient was then weaned from cardiopulmonary bypass. Arterial blood gas levels demonstrated a significant improvement in the oxygenation (Po_2 of 375 torr, Fio_2 of 1.00). The right heart was also significantly less distended and now contracted vigorously on a much lower dose of inotropic agents (dobutamine, 7 μg/kg/min).

After protamine reversal of heparinization it was apparent that a severe coagulopathy was present that necessitated multiple transfusions of blood components. Subsequent analysis of blood drawn preoperatively revealed evidence of severe disseminated intravascular coagulation (Table I). While hemostasis was being obtained in the mediastinum, the abdominal girth was noted to be enlarging. Abdominal paracentesis revealed bleeding, and an exploratory laparotomy was done through a midline incision. Several small bleeding points were oversewn along the hysterotomy incision, resulting in control of the hemorrhage. Both incisions were then closed. Repetition of the coagulation profile 4 hours after operation demonstrated complete resolution of the disseminated intravascular coagulation (Table I).

On the second postoperative day a Greenfield filter was placed in the inferior vena cava as prophylaxis against any further emboli. Repeat lung scan done 3 weeks after operation revealed a restoration of perfusion to the left upper lobe and minimal perfusion to the left lower lobe (Fig. 1, *B*). Oral anticoagulation was begun and continued for 3 months; repeat lung perfusion scan done then demonstrated complete return of blood flow to the left lung (Fig. 1, *C*). The patient has returned to a fully normal and productive life without any residual disability.

Table I. Coagulation profile

	Preoperative	*Postoperative*
Prothrombin time (sec)	22.4	13.8
Partial thromboplastin time (sec)	71.0	44.9
Coagulation factor (%)		
II	37	34
V	49	52
VII-X	52	78
Fibrinogen	151	333
TRCH II	22.4	2.8
3P test	+	—

TRCH, Tanned red cell hemagglutination inhibition; *3P,* test for fibrin monomers.

*Four hours after operation.

Comment

Traditionally the diagnosis of amniotic fluid embolism has been made by postmortem examination of the pulmonary artery contents. Demonstration of fetal cells in this specimen is considered to be pathognomonic of this disorder. Antemortem diagnosis has been confined to the finding of fetal squamous cells in the maternal circulation retrieved either through a central venous or pulmonary artery catheter; however, this method is imprecise because of a high false-positive yield.[3] Therefore extraction of the pulmonary artery thrombus during pulmonary thrombectomy and subsequent pathologic examination represents the most accurate means of establishing the diagnosis during life. Of greater importance is the ability to immediately relieve the pulmonary arterial obstruction by removal of the thromboembolus. Although restoration of the blood flow to

the lung was incomplete in our patient as demonstrated by early postoperative perfusion scan, it was not clinically significant because there was prompt reversal of the intrapulmonary shunting and a greatly diminished need for inotropic support. In this case, the limited perfusion of the left lower lobe most likely represents thrombosis of small pulmonary arterioles that were not accessible to thrombectomy. The outcome may have been affected more favorably had thrombectomy been performed earlier. Nonetheless, by 3 months after operation the pulmonary blood flow had returned to a completely normal level.

Severe life-threatening hemorrhage is another characteristic of amniotic embolism that occurs in 40% of such patients.[1] The prominent feature appears to be disseminated intravascular fibrin deposition in response to the procoagulant effect of amniotic fluid. The coagulation profiles performed in our patient illustrate this point. Preoperatively there was evidence of disseminated intravascular coagulation, which was completely reversed by 4 hours after operation. Although this dramatic improvement coincides with the administration of blood components, it is certain that the removal of the procoagulant stimulus by thrombectomy was beneficial in reversing the coagulopathy. Furthermore, treatment of the coagulopathy by simple replacement therapy without removal of the thrombogenic stimulus may aggravate the pulmonary vascular obstruction by causing continued thrombogenesis and resulting in progressive arterial desaturation and right heart failure.

In conclusion, on the basis of this case report, emergent pulmonary thrombectomy for postpartum shock caused by amniotic fluid embolism is helpful in establishing a diagnosis in vivo, restoring pulmonary blood flow and normal physiologic function as arterial oxygenation, normal right heart function, and hemodynamic stability, and reversing a life-threatening coagulopathy. Further application of this technique is indicated to fully assess its merit.

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Antiphospholipid antibodies and recurrent pregnancy loss: Correlation between the activated partial thromboplastin time and antibodies against phosphatidylserine and cardiolipin

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Concordance was determined among the presence of the lupus anticoagulant measured by prolongation of the activated partial thromboplastin time and IgG and IgM antibodies against phosphatidylserine and cardiolipin in 47 patients selected for study because of histories of recurrent spontaneous pregnancy loss and a positive test for at least one antiphospholipid antibody. Forty-five of 47 patients (96%) had a prolonged activated partial thromboplastin time, ranging from 46 to 150 seconds. Elevated levels of IgG antiphosphatidylserine antibodies and IgM antiphosphatidylserine antibodies were present in 41 (87%) and in 19 (40%) of samples, respectively. Antibodies against cardiolipin were less commonly observed; IgG anticardiolipin antibodies in only 32 (68%) of 47 samples and IgM anticardiolipin antibodies in 15 (36%) of 42 samples. Neither the level of IgG antiphosphatidylserine antibodies nor the level of IgG anticardiolipin antibodies correlated well with the degree of prolongation of coagulation in the activated partial thromboplastin time ($R = 0.312$, $p = 0.032$ for IgG antiphosphatidylserine antibodies versus activated partial thromboplastin time; $R = 0.251$, $p = 0.088$ for IgG anticardiolipin antibodies versus activated partial thromboplastin time). Concordance with the activated partial thromboplastin time, however, was observed in 41 (87%) samples for IgG antiphosphatidylserine antibodies and in only 32 (68%) samples for IgG anticardiolipin antibodies. Our conclusion is that the antiphosphatidylserine assay correlates best, although not totally, with the presence of lupus anticoagulant and that the antiphosphatidylserine assay is more sensitive than testing for anticardiolipin. (Am J Obstet Gynecol 1990;163:575-84.)

Key words: Recurrent pregnancy loss, autoimmune disease, lupus anticoagulant, antiphospholipid antibodies, anticardiolipin antibody, antiphosphatidylserine antibody, activated partial thromboplastin time

The production of autoantibodies directed against membrane phospholipids has been strongly associated with a variety of medical disorders including thromboembolic disease, recurrent pregnancy loss, intrauterine growth retardation, severe pregnancy-induced hypertension, and thrombocytopenia.[1-5] Patients with this autoimmune disorder may produce an antibody, or a family of antibodies, that can be measured either by prolongation of in vitro phospholipid–dependent coagulation tests, by an enzyme-linked immunosorbent assay (ELISA) using crude extracts of human brain as antigen,[6, 7] or by ELISAs or radioimmunoassays (RIAs) using acidic phospholipids as antigens.[8-10] The lupus anticoagulant was the first antiphospholipid antibody described and remains the standard against which all other assays are compared.[11, 12] The recommended approach to convincingly determine the presence of the lupus anticoagulant should include a screening test for prolonged coagulation and the identification of the presence of an inhibitor.[13] Although patients with factor VIII inhibitors can usually be differentiated clinically by a tendency for prolonged bleeding rather than thrombosis, a confirmatory test addressing the antiphospholipid nature of the inhibitor may be incorporated into the testing. Lupus anticoagulant is detected in most laboratories by the prolongation of the activated partial thromboplastin time (APTT). The APTT, however, has been labeled less sensitive than other screening tests primarily for two reasons: the test is prone to the effects of altered levels of normal coagulation factors, which may be elevated during pregnancy, and the content of procoagulatory phospholipids, especially phosphatidylserine, may vary considerably among com-

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mercially available preparations of partial thromboplastin.[13] In addition, the APTT is cumbersome and the specificity and class of the antibody that prolongs coagulation cannot be readily identified.

Recently many laboratories have proposed that adequate diagnosis of this autoimmune disorder can be made by means of an assay for the anticoagulant activity plus an ELISA for antibody against cardiolipin.[14] In one of the original studies a good correlation was observed between the amount of IgG antibody against cardiolipin and the degree of prolongation of coagulation in the kaolin clotting assay.[14] In most studies, however, the prolongation of coagulation does not correlate well with the degree of reactivity in any ELISA, including assays in which partial thromboplastin is used.[6, 7, 10, 12] We and others have previously suggested that measurement of antibodies against another phospholipid, phosphatidylserine, may be as good as, if not superior to, the use of assays for anticardiolipin.[10, 12]

To investigate the relative efficacy of immunoassays for antiphosphatidylserine and anticardiolipin we used quantitative ELISA techniques and investigated the relationship of antiphosphatidylserine antibodies and anticardiolipin antibodies to the incidence of lupus anticoagulant in 47 women with recurrent pregnancy loss.

Patients and methods

Patients. We studied serum samples obtained from 47 women who were selected from patients referred to the Obstetric Clinic at the University of Utah Medical Center for evaluation of recurrent pregnancy loss. All patients had at least two consecutive pregnancy losses, and only seven had a diagnosis of systemic lupus erythematosus. The patients were selected on the basis of a positive test for at least one antiphospholipid antibody: either the presence of lupus anticoagulant or an IgG or IgM antibody against phosphatidylserine or cardiolipin. Serum from five patients was not available for testing for IgM antibody against cardiolipin, although in each case the patient had positive results for the lupus anticoagulant and IgG antibody against cardiolipin.

Plasma for the coagulation studies was collected in sodium citrate tubes (0.015 mol/L buffered citrate, Becton-Dickinson Vacutainer Systems, Rutherford, N.J.) by venipuncture and the coagulation assay was performed within 2 hours. Serum was obtained by venipuncture in Vacutainer blood collecting tubes without anticoagulants (Becton-Dickinson) at the same time as the coagulation sample was drawn. The blood was allowed to clot at room temperature and was then centrifuged at 175 *g* for 10 minutes. The serum was aspirated with a plastic pipette and stored in 1 ml aliquots in polyethylene tubes at −70 C° until use.

Laboratory methods. The lupus anticoagulant was present when the patient's plasma demonstrated prolongation of the activated partial thromboplastin time without correction by the addition of normal plasma at a ratio of 1:1. The APTT was performed in the Coagulation Laboratory at the University of Utah with a partial thromboplastin prepared from human brain as described previously.[10] Preparations of partial thromboplastin were titrated against a battery of normal plasma so that a coagulation time of longer than 45 seconds was considered abnormally prolonged.

Antibodies against cardiolipin and phosphatidylserine were measured by an ELISA procedure that has been previously described.[5, 15, 16] Immulon I, 96-well microtiter plates (Dynatech Labs, Alexandria, Va.) were prepared by diluting the individual phospholipids (Sigma Chemicals, St. Louis) in absolute ethanol to a final concentration of 45 μg/ml and adding 30 μl to each well. The solvent was allowed to evaporate overnight at room temperature. Nonspecific binding was blocked by addition of 130 μl of a 10% solution of fetal bovine serum (Gibco, Buffalo, N.Y.) in phosphate-buffered saline solution (pH 7.2 to 7.4) to each well and incubating at 20° to 25° C for 1 hour. The plates were washed three times with fetal bovine serum–phosphate-buffered saline solution with 1- to 2-minute incubation periods during the washes. After incubation 100 μl of a 1:32 dilution of each serum was added in duplicate and incubated for 1 hour at 20° to 25° C. After three washings 100 μl of goat anti-human IgG (1:500 dilution) or goat anti-human IgM (1:1000 dilution) (Fc fragment–specific, Cooper Biomedical, Malvern, Pa.) was added and incubated at 20° to 25° C for 1 hour. After three washings 100 μl of a 1:800 dilution of peroxidase conjugated rabbit anti-goat IgG (Fc fragment–specific, Cooper Biomedical) was added to each well and the plates incubated for 1 hour. The plates were washed three times and color development was induced by adding 100 μl of an indicator (one volume of 0.05% hydrogen peroxide plus nine volumes of 0.08% 5-amino salicylic acid, pH 6.0) and incubated for 15 minutes. Color development was stopped with 30 μl of 1N sodium hydroxide and the optical density was read at 450 nm on a Microplate Autoreader (Bio-Tek Instruments, Inc, Winooski, Vt.).

All spectrophotometric readings were adjusted by subtracting the readings observed on nonspecific-binding plates (plates that did not receive phospholipid although they were processed in an identical fashion) and converting the resultant values to standard deviations above the mean (SD) by use of the current means and standard deviations of the optical densities from an ongoing accumulation in our laboratory of more than 1000 normal control individuals. Each plate contained laboratory positive control sera that were validated against externally provided reference sera. The

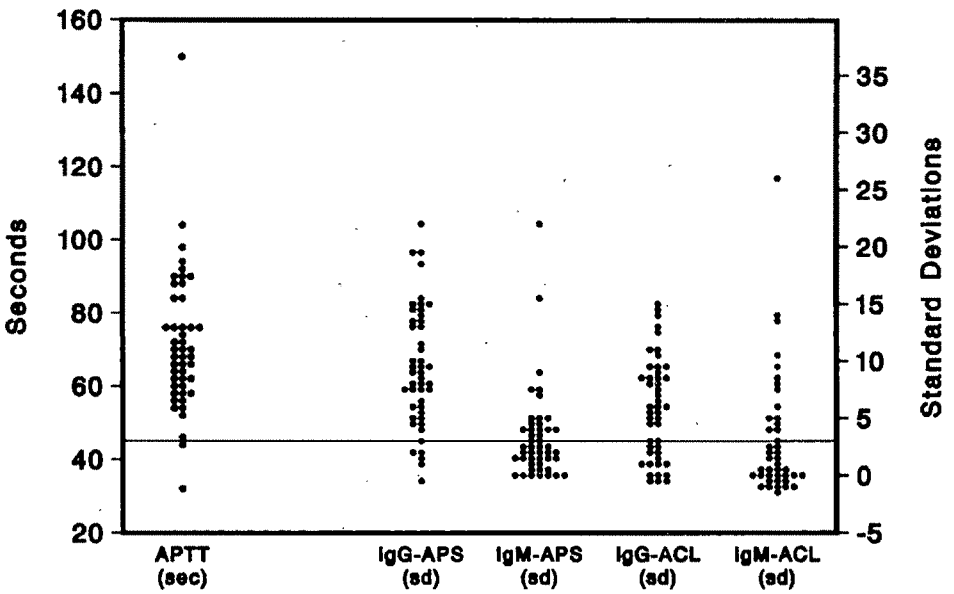


Fig. 1. Distribution of the APTT, IgG and IgM antibodies against phosphatidylserine *(IgG-APS* and *IgM-APS)*, and IgG antibodies against cardiolipin *(IgG-ACL)* in 47 patients with a history of recurrent pregnancy loss. Forty-two of these patients were also tested for IgM antibodies against cardiolipin *(IgM-ACL)*. The APTT is expressed in seconds and the other assays are expressed in standard deviations above the mean of the normal controls. The horizontal line denotes the upper limit of normal in all assays (45 seconds or 3 SDs).

Table I. APTT and levels of IgG and IgM antibodies against phosphatidylserine and cardiolipin in women with recurrent pregnancy loss

*Antiphospholipid antibody assay**	*Range*	*Mean*	*SD*	*Median*	*Positive†* *(%)*
APTT (sec)	32-150	71	19	67	96
IgG antiphosphatidylserine (SD)	−0.9-22.1	9.5	5.3	8.8	87
IgM antiphosphatidylserine (SD)	−0.5-21.8	3.3	4.0	2.4	40
IgG anticardiolipin (SD)	−1.0-15.2	5.9	4.5	5.8	68
IgM anticardiolipin (SD)	−1.8-26.0	3.1	5.5	1.2	36

*47 samples were assayed, except for IgM anticardiolipin, in which only 42 were available.

†For the APTT positive is defined as >45 seconds, and for the ELISAs positive is defined as >3 SD above the mean of the normal controls.

means and standard deviations used for each assay are as follows: IgG antiphosphatidylserine, 0.037 ± 0.022; IgM antiphosphatidylserine, 0.032 ± 0.027; IgG anticardiolipin, 0.070 ± 0.033; and IgM anticardiolipin, 0.046 ± 0.019.

The means between each group were compared with the Wilcoxon signed-rank test for paired samples. Correlations between individual tests were calculated with the Spearman rank method. Proportions from the paired samples were analyzed with the exact binomial distribution on the untied samples.

Results

All available patient samples were evaluated for antiphospholipid antibodies by the APTT and ELISAs for IgG and IgM antibodies against phosphatidylserine, and cardiolipin (Fig. 1 and Table I). The APTT values ranged from 32 seconds to 150 seconds; a coagulation time of longer than 45 seconds was considered abnormal. Plasma from 45 of the 47 patients (96%) had a prolonged APTT, none of which corrected on the addition of normal plasma. Of antibodies tested by ELISA, IgG antiphosphatidylserine antibodies were the most prevalent; 87% of the samples were >3 SD above the mean of our normal controls and the median level was 8.8 SDs. IgM antiphosphatidylserine antibodies were less prevalent; 40% of the samples were elevated and the median level was 2.4 SDs. IgG anticardiolipin antibodies were also present in most patients; 68% of the samples were positive with a median of 5.8 SDs.

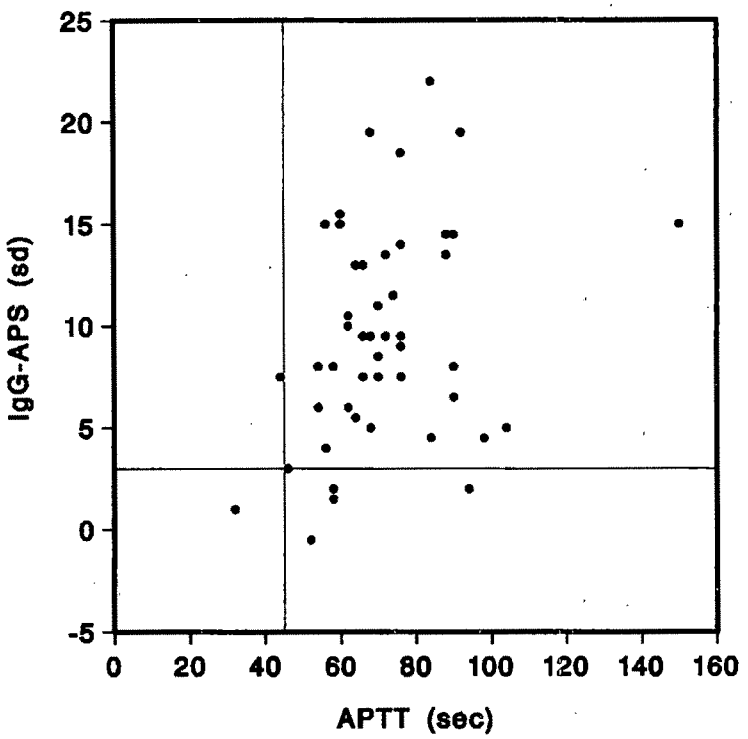


Fig. 2. Scatterplot shows the levels of IgG antibodies against phosphatidylserine (*IgG-APS* on the *Y* axis, expressed in standard deviations above the mean of normal controls) and the APTT (on the *X* axis, expressed in seconds) in 47 patients with recurrent pregnancy loss. Regression line: $Y = 0.087X + 3.299$; $R = 0.312$; $p = 0.03$.

The assay for IgM anticardiolipin antibodies had the lowest frequency of positive results (36%) with a median of 1.2 SDs. All paired ELISA results were significantly different ($p < 0.05$) from each other with the exception of IgM antiphosphatidylserine antibodies versus IgM anticardiolipin antibodies.

The amount of both IgG antiphosphatidylserine antibodies and IgG anticardiolipin antibodies correlated weakly with the degree of prolongation of coagulation in the APTT (Figs. 2 and 3). When compared with the prolongation of the APTT, IgG antiphosphatidylserine antibodies had a correlation coefficient of 0.312 ($p = 0.032$) and the IgG anticardiolipin antibodies had a correlation coefficient of 0.251 ($p = 0.088$).

Concordance between the APTT and each of the ELISAs for antibodies against phosphatidylserine and cardiolipin can also be seen in Figs. 2 and 3. The results of the APTT were accurately predicted by the presence or absence of IgG antiphosphatidylserine antibodies in 41 of 47 (87%) samples (40 samples were positive by both assays and one sample was negative by both). Six samples were not in agreement; five were prolonged in the APTT and negative for IgG antiphosphatidylserine antibodies and one had a normal APTT and elevated IgG antiphosphatidylserine. The assay for IgG anticardiolipin antibodies agreed less well with the APTT, with only 32 (68%) samples in which the APTT and the assay for IgG anticardiolipin antibodies agreed (31 were positive in both assays and one was negative for both). In 15 samples, however, the APTT was not accurately predicted by the assay for IgG anticardiolipin antibodies; 14 of the samples had prolonged clotting times and were negative for IgG anticardiolipin antibodies, whereas one sample that was positive for IgG anticardiolipin antibodies had a normal clotting time. The difference between the concordance of IgG antiphosphatidylserine antibodies and IgG anticardiolipin antibodies with the APTT was significant at $p = 0.04$. When IgG and IgM antibodies were simultaneously evaluated both assays improved in capacity to predict the APTT; combined assays for IgG antiphosphatidylserine antibodies and IgM antiphosphatidylserine antibodies was inaccurate in only four samples, whereas combined assays for IgG anticardiolipin antibodies and IgM anticardiolipin antibodies was inaccurate in 12 samples. The difference between antiphosphatidylserine and anticardiolipin combined IgG and IgM assays was significant at $p = 0.03$. Sensitivity of the combined IgG and IgM assays for antiphosphatidylserine in relationship to prolongation of the APTT was 91%, whereas the sensitivity of the assays for anticardiolipin was 73%.

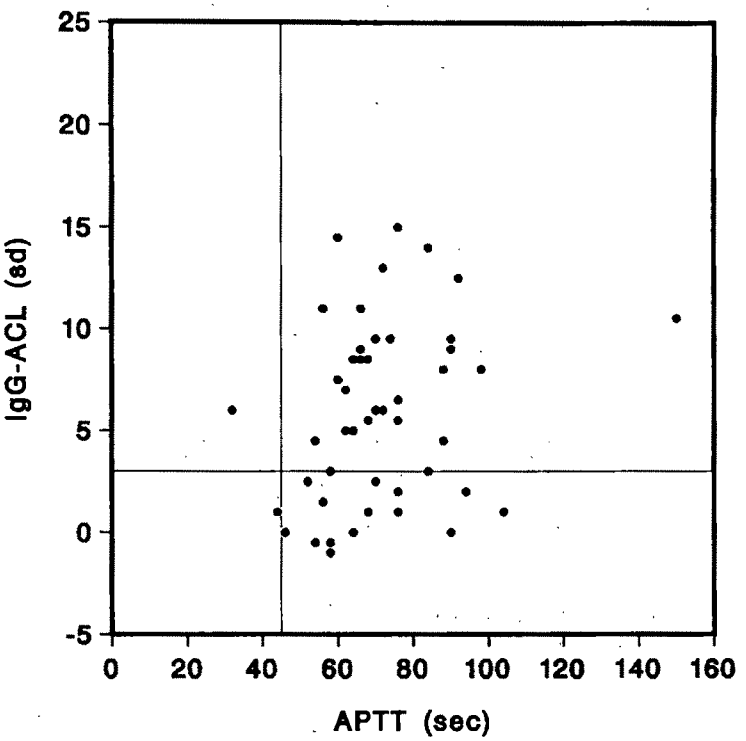


Fig. 3. Scatterplot shows the levels of IgG antibodies against cardiolipin (*IgG-ACL* on the *Y* axis, expressed in standard deviations above the mean of normal controls) and the APTT (on the *X* axis, expressed in seconds) in 47 patients with recurrent pregnancy loss. Regression line: $Y = 0.059X + 1.656$; $R = 0.251$; $p = 0.09$.

The best correlations were observed when antibodies of the same class were compared. The amount of IgG antiphosphatidylserine antibodies correlated well with the amount of IgG anticardiolipin antibodies ($R = 0.665$, $p < 0.001$) (Fig. 4). Several samples, however, contained one specificity without the other; eleven (23%) specimens were negative for IgG anticardiolipin antibodies yet had elevated amounts of IgG antiphosphatidylserine antibodies, although these elevations were never greater than 9 SDs. Only two (4%) samples had IgG anticardiolipin antibodies without elevated IgG antiphosphatidylserine antibodies, and both had relatively low amounts of IgG anticardiolipin antibodies (3.2 and 6.0 SD).

The best comparison was between assays for IgM antiphosphatidylserine antibodies and IgM anticardiolipin antibodies ($R = 0.749$, $p < 0.001$) (data not shown). This may be somewhat misleading because the plurality (23 or 48.9%) of the samples were negative for both antibodies and comparison of the positive samples was not as significant ($R = 0.671$, $p = 0.031$). None of the other correlations were statistically significant (R values between 0.239 and -0.143).

Tables II and III allow simultaneous comparisons of all three assays. Table II compares in a pair-wise fashion the proportion of samples in agreement between IgG antiphosphatidylserine antibodies and APTT with the proportion in agreement between IgG anticardiolipin antibodies and APTT. In 35 patients, both pairs of tests were concordant; i.e., in 30 patients the APTT, assays for IgG antiphosphatidylserine antibodies, and assays for IgG anticardiolipin antibodies all agreed on the presence of antiphospholipid antibody, and in an additional five patients, assays for IgG antiphosphatidylserine antibodies and IgG anticardiolipin antibodies both disagree with the APTT results. In 11 of the 12 remaining patients, the assay for IgG antiphosphatidylserine antibodies agreed with the APTT, whereas the assay for IgG anticardiolipin antibodies did not ($p < 0.003$ by an exact binominal test with the probability of agreement = 0.5). The single sample in which the assay for IgG anticardiolipin antibodies was concordant with the APTT, whereas the assay for IgG antiphosphatidylserine antibodies was not concordant, was from a patient with multiple pregnancy losses, a normal APTT, negative assays for IgG anticardiolipin antibodies and IgM anticardiolipin antibodies, and a positive assay for IgG antiphosphatidylserine antibodies.

Table III compares in a similar fashion the proportion of samples in concordance with the APTT using either IgG or IgM antiphosphatidylserine antibodies and IgG or IgM anticardiolipin antibodies. The anti-

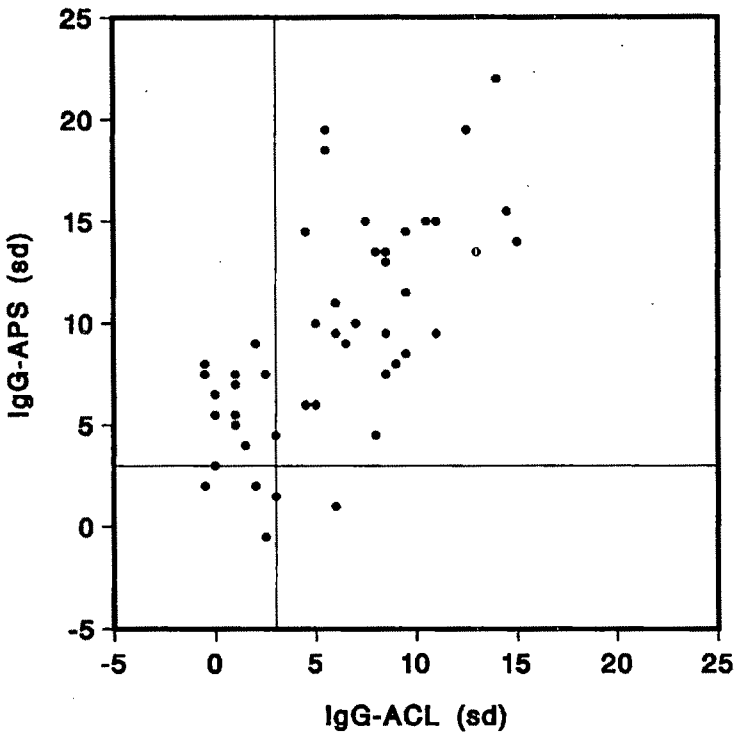


Fig. 4. Scatterplot shows the levels of IgG antibodies against phosphatidylserine (*IgG-APS* on the *Y* axis, expressed in standard deviations above the mean of normal controls) and the levels of IgG antibodies against cardiolipin (*IgG-ACL* on the *X* axis, expressed in standard deviations above the mean of normal controls) in 47 patients with recurrent pregnancy loss. Regression line: $Y = 0.780X + 4.864$; $R = 0.665$; $p < 0.001$.

phosphatidylserine assay is significantly more concordant with the APTT than is the anticardiolipin assay ($p = 0.03$). The incorporation of IgM antiphosphatidylserine antibodies lowers the number of samples that show lack of concordance between antiphosphatidylserine and APTT from six (Table II) to four. Therefore two samples had prolonged APTTs with IgM antiphosphatidylserine antibodies without accompanying IgG antiphosphatidylserine antibodies. Of the remaining four that show lack of concordance, one has a normal APTT with the presence of antiphosphatidylserine and three have prolonged APTTs with normal levels of antiphosphatidylserine. The incorporation of IgM anticardiolipin antibodies decreased the number of samples that show lack of concordance between the anticardiolipin assay and APTT from 16 to 12; therefore four samples had prolonged APTTs and IgM anticardiolipin antibodies, without IgG anticardiolipin antibodies. The number of samples with complete concordance among APTT, anticardiolipin, and antiphosphatidylserine increased from 30 to 32, indicating that two samples with prolonged APTTs were negative for IgG antibodies against either phosphatidylserine or cardiolipin but contained IgM antibodies against both phospholipids. Two additional samples show a lack of concordance between the APTT and the antiphosphatidylserine assays, yet are concordant between the APTT and anticardiolipin assays. These samples therefore were characterized by prolonged APTTs and the presence of IgM anticardiolipin antibodies, without IgG anticardiolipin antibodies, IgG antiphosphatidylserine antibodies, or IgM antiphosphatidylserine antibodies.

Comment

In this study we focused on 47 women who were referred to our clinic with a history of recurrent pregnancy loss. Only seven patients were diagnosed as also having signs of systemic lupus erythematosus. This patient population immediately sets our study apart from most of the published studies on antiphospholipid antibodies, which described patient populations containing larger proportions of patients with systemic lupus erythematosus. However, in our experience the majority of patients referred for pregnancy loss associated with antiphospholipid antibodies do not have systemic lupus erythematosus. The purpose of this study was to compare the diagnostic efficacy of ELISA procedures for antibodies against cardiolipin and phosphatidylserine as an adjunct to assays for anticoagulant activity. These 47 patients were selected, therefore, because of a history of recurrent pregnancy loss and the presence of an antiphospholipid antibody by a positive reaction

Table II. Concordance between results of IgG antiphosphatidylserine and APTT versus concordance between results of IgG anticardiolipin and APTT

IgG-ACL concordance with APTT	*IgG antiphosphatidylserine concordance with APTT*	
	Yes	*No*
Yes	30	1
No	11	5

$p = 0.003$. Elevations are defined as >45 seconds in the APTT and >3 SD in IgG antiphosphatidylserine and IgG anticardiolipin ELISA tests.

Table III. Concordance between results of IgG or IgM antiphosphatidylserine and APTT versus concordance between results of IgG or IgM anticardiolipin and APTT

IgG or IGM anticardiolipin concordance with APTT	*IgG or IgM antiphosphatidylserine concordance with APTT*	
	Yes	*No*
Yes	32	3
No	11	1

$p = 0.03$. Elevations are defined as >45 seconds in the APTT and >3 SD in IgG or IgM antiphosphatidylserine and IgG or IgM anticardiolipin ELISA tests.

in any of the five assays described in this study; the APTT, IgG and IgM antibodies against cardiolipin, and IgG and IgM antibodies against phosphatidylserine. The patients consisted of a mixture of women with primary and secondary abortions with pregnancy losses in both the second and first trimester. There was no significant correlation between reactivity in any of our laboratory tests and any clinical manifestation, including a history of thrombosis or timing of pregnancy loss. Many more patients with recurrent pregnancy loss were tested and had negative results in all five tests.

Previously reported results of patients with systemic lupus erythematosus appear contradictory. Our data agree with Meyer et al.,[17] who observed relatively good correlation coefficients of 0.47 and 0.64 between levels of anticardiolipin antibodies and prolongation of the APTT, and between levels of antiphosphatidylserine antibodies and the APTT, respectively. Other studies, however, have reported in patients with systemic lupus erythematosus that 24% had lupus anticoagulant without anticardiolipin and 42% had elevated levels of anticardiolipin without lupus anticoagulant, and that there was no correlation between APTT values and anticardiolipin levels (correlation coefficient of 0.0057).[18] Results from other groups who studied primarily patients with systemic lupus erythematosus have shown that 55% to 100% of patients with positive lupus anticoagulant results have raised levels of IgG anticardiolipin antibodies and 35% to 86% of patients with positive IgG anticardiolipin antibodies results have lupus anticoagulant, depending on the particular assay used to detect lupus anticoagulant.[19-21] Sensitivity of the anticardiolipin assay for detecting lupus anticoagulant was approximately 77%.[21] One recent study included 100 patients with positive lupus anticoagulant results, of whom only eight had recurrent pregnancy loss.[12] Only 73% of the patients had detectable IgG or IgM antibodies, or both, against one of four phospholipids (cardiolipin, phosphatidylserine, phosphatidic acid, or phosphatidylinositol). Of these, 29% had IgG antibodies alone, 56% had both IgG and IgM antibodies, and 15% had IgM antibodies alone. Distribution of antiphospholipid antibodies was as follows: anticardiolipin, 61%; antiphosphatidylserine, 60%; antiphosphatidic acid, 54%; and antiphosphatidylinositol, 47%. Nine patients had a positive reaction against a single phospholipid (three against cardiolipin, two against phosphatidylserine, four against phosphatidylinositol). These results agree with some of our previous observations that sera from patients with positive lupus anticoagulant results most commonly contained antibodies against phosphatidylserine and cardiolipin, with 40% having IgG antibodies alone and 60% having IgG and IgM antibodies, and that many patients also had antibodies against a large number of other phospholipids: 80% against phosphatidylethanolamine, 80% against phosphatidylglycerol, and 67% against phosphatidylinositol.[10]

The recommended approach to convincingly determine the presence of the lupus anticoagulant should include a screening test for prolonged coagulation and the identification of the presence of an inhibitor.[13] At least four screening tests are currently available and the advantages and disadvantages of each have been recently thoroughly reviewed.[13] We usually recommend the activated partial thromboplastin time to screen for the lupus anticoagulant because clinicians are familiar with it and the test is widely available. The activated partial thromboplastin time, however, has been labeled less sensitive than other screening tests primarily for two reasons: the test is prone to the effects of altered levels of normal coagulation factors, which may be elevated during pregnancy, and the content of procoagulatory phospholipids, especially phosphatidylserine, may vary considerably among commercially available preparations of partial thromboplastin.[13] However, if the activated partial thromboplastin time is used to test patients who are not currently pregnant, which is the

majority of patients being evaluated, the problem of pregnancy-associated elevations in the levels of coagulation factors can be avoided. In addition, the laboratory must be sensitive to variations in batches of partial thromboplastin and titer each preparation to standardize the assay. Personnel of the Coagulation Laboratory at the University of Utah, where the APTT described in this study was performed, prepare and carefully standardize their own partial thromboplastin extracted by chloroform/methanol from human or bovine brain; this process results in a very sensitive, reproducible, and specific reagent. Therefore the incidence of lupus anticoagulant in this report is characteristic only of that particular laboratory and would, most likely, vary considerably from laboratory to laboratory.

Mixing studies are usually performed to determine the presence of an inhibitor and exclude the possibility of a coagulation factor deficiency. Abnormal plasma is retested after mixing with an equal volume of normal plasma; the APTT will not correct in the presence of lupus anticoagulant. Even with the most potent anticoagulant, some correction of the clotting time is expected, and laboratories must establish guidelines for defining a significant correction.[13] In our coagulation laboratory the presence of lupus anticoagulant is established when the APTT fails to correct to less than the control mean + 2 SDs.

The question of the specificity of antibodies against phospholipids remains to be resolved. The most widely accepted concept is that antiphospholipid antibodies are cross reactive against acidic phospholipids and potentially against other negatively charged phosphorus-containing molecules. Most of the information has been accumulated, however, with monoclonal antibodies generated from mice prone to systemic lupus erythematosus or patients with systemic lupus erythematosus, or by using polyclonal sera from a small number of patients, usually with systemic lupus erythematosus.[17, 22-24] No doubt most patients produce a cross-reactive antibody, but there is heterogeneity among patients, and some may be producing monospecific antibodies. We reported previously that although most patients produce antibodies that react with both phosphatidylserine and cariolipin, a few patients will produce high titers of antibody that react only with phosphatidylserine.[10]

In a recent publication that reported on patients who were undefined with regard to systemic lupus erythematosus status and were selected for IgG, IgM, or IgA positive reactions against cardiolipin and later tested for IgG antiphosphatidylserine antibodies they calculated a correlation coefficient between IgG anticardiolipin antibodies and IgG antiphosphatidylserine antibodies of 0.84.[25] Although their interpretation was that testing for antiphosphatidylserine afforded little apparent advantage over testing for anticardiolipin, closer analysis of the data shows that more patients were positive for IgG antiphosphatidylserine antibodies than for IgG anticardiolipin antibodies. Two (5.3%) of the patients had elevated assays for IgG antiphosphatidylserine antibodies without IgG anticardiolipin antibodies, whereas none had IgG anticardiolipin antibodies without an accompanying elevation of IgG antiphosphatidylserine antibodies.

In this study most patients have antibodies against both phosphatidylserine and cardiolipin. Five patients, however, have levels >5 SD of IgG antiphosphatidylserine antibodies without corresponding elevations in IgG anticardiolipin antibodies and only one patient has levels >5 SD of IgG anticardiolipin antibodies without elevations in IgG antiphosphatidylserine antibodies. If every patient produced crossreactive antibodies, each patient's serum would be expected to have similar reactivity against both phosphatidylserine and cardiolipin. However, these data suggest that a small group of patients produce antibodies that predominantly react with either phosphatidylserine or cardiolipin and which may not be cross-reactive. There is at least one report of the production in rabbits of antiphosphatidylserine antibodies that did not crossreact with cardiolipin, phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol, or sphingomyelin.[26] In addition, we have produced a battery of mouse monoclonal antibodies that can be classified into one of three groups: those that are reactive with phosphatidylserine and not with cardiolipin, reactive with cardiolipin and not with phosphatidylserine, and crossreactive with both cardiolipin and phosphatidylserine[16] (Rote et al., unpublished observations).

To understand the biologic effects of antiphospholipid antibodies, their antigenic targets and how the antibody affects biologic activity must eventually be understood. Antiphospholipid antibodies most likely affect alterations in either platelets or endothelial cell-mediated homeostasis of blood clotting.[3, 27] Antibody specificity against cardiolipin, although useful in the diagnosis of the antiphospholipid antibody syndrome, cannot explain the pathophysiology of the disease. It appears highly unlikely that cardiolipin is the target antigen for any of the biologic activities associated with antiphospholipid antibodies. Phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine are principal components of plasma membranes, whereas cardiolipin has very restricted distribution, localized primarily, if not exclusively, in the inner mitochondrial membrane and not exposed, in a living cell, to circulating antiphospholipid antibodies. For a living cell to be affected in situ by antiphospholipid antibodies, the target antigen must be present in an adequate

concentration in the plasma membrane. Cardiolipin does not meet that criterion.

The mechanism by which antiphospholipid antibodies prolong coagulation in the APTT appears to be through binding to phospholipid within the partial thromboplastin, preventing assembly of the prothrombin-prothrombinase complex, which is necessary for efficient activation of the coagulation cascade.[3,27] Although it has been suggested that affinity-purified anticardiolipin can prolong in vitro coagulation, the actual data have rarely been fully described.[28-30] Exner et al.[30] have been able to separate partially anticardiolipin and lupus anticoagulant activity on an affinity column containing cardiolipin. In addition, cardiolipin is not generally found in the partial thromboplastin used to determine lupus anticoagulant activity by the APTT. With immunologic staining of partial thromboplastin separated by thin-layer chromatography we have determined that the phosphatidylserine constituent is the primary component that reacts with antiphospholipid antibodies from patients with lupus anticoagulant and recurrent pregnancy loss.[16,32] Although determination of antiphosphatidylserine and anticardiolipin may be useful diagnostically, detection of antiphosphatidylserine may be more relevant to understanding the mechanism of this particular autoimmune phenomenon.

It is our conclusion that rigorous testing for lupus anticoagulant activity with well-calibrated and dependable reagents is adequate for detecting most patients with antiphospholipid antibody–associated recurrent pregnancy loss. Most commercially available reagents, however, are too variable to adequately define lupus anticoagulant by the APTT, thus specific phospholipid ELISAs must also be used. Although testing for antibodies against cardiolipin may provide some insight into patients with the antiphospholipid antibody syndrome, testing for antibody against phosphatidylserine identifies some patients who are nonreactive for anticardiolipin and lupus anticoagulant and measures an antibody specificity that is a prime candidate for explaining the pathophysiologic mechanisms of the disease.

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Effect of mitral valve prosthetic surgery on the outcome of a growth-retarded fetus

A case report

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Mitral valve prosthetic surgery was performed at 29 weeks' gestation in a woman who had reoperation for a thrombotic mitral valve prosthesis and pulmonary edema. Concomitant severe preeclampsia was also present. During operation fetal bradycardia developed and the fetus died. Because the findings differ from those previously reported with regard to normal pregnancies, their implications are discussed. (Am J Obstet Gynecol 1990;163:584-6.)

Key words: Mitral valve surgery, pregnancy, growth-retarded fetus

Most acquired valvular lesions of the heart are rheumatic in origin, and mitral stenosis is the most common valvular lesion encountered during pregnancy. Morbidity and mortality result from congestive heart failure or arrhythmias.[1] Cardiac surgery can be performed during pregnancy with excellent results for the mother and at relatively low risk to the fetus.[2]

We report a patient with a previous history of mitral valve replacement who had an operation during pregnancy for a thombosed mitral valve and pulmonary edema whose fetus was growth retarded.

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Case report

A 33-year old Native American woman, gravida 3, para 3, was seen on Oct. 6, 1988, at 27 weeks' gestation (by her last menstrual period and a 10-week ultrasonogram). She was transferred to the University of New Mexico Hospital because she was thought to have congestive heart failure. She had a history of rheumatic fever with mitral stenosis and aortic insufficiency diagnosed in 1982 when she developed pulmonary edema post partum. She then underwent mitral and aortic valve replacement with Lillehei-Kaster prosthesis (Medical Inc., Inver Grove Heights, Minn.). In 1984 pulmonary edema again developed after a second-trimester pregnancy loss. Since then she had been treated with coumadin until approximately 12 weeks



Fig. 1. Presence of decelerations during operation.

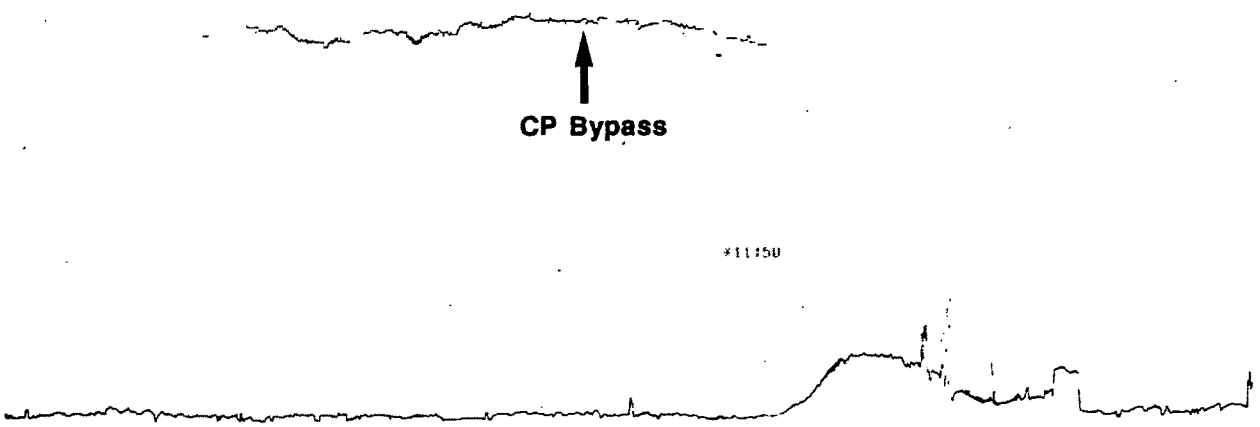


Fig. 2. Patient connected to cardiopulmonary bypass and disappearance of fetal heart rate.

into her third pregnancy, when her medication was changed to subcutaneous heparin. On admission to the University of New Mexico Hospital, she had two-pillow orthopnea and reported progressively worsening shortness of breath on exertion since the first trimester of pregnancy. Blood pressure was 150/110 mm Hg and results of a urinalysis showed 8 gm of protein in a 24-hour collection. Chest x-ray films revealed no evidence of acute disease. A transthoracic echocardiogram showed moderate mitral stenosis, mild aortic insufficiency, and mild left ventricular dysfunction with no apparent thrombus. Obstetric ultrasonography revealed all growth parameters consistent with a 24-week fetus with an estimated fetal weight of 580 gm. This parameter was below the 10th percentile for weight, consistent with intrauterine growth retardation.

The patient was managed conservatively with bed rest and close surveillance. The hypertension responded to bed rest and the patient did not require antihypertensive medication. Proteinuria remained without significant change on repetitive 24-hour urine collections. Laboratory studies remained unremarkable except for elevated serum uric acid and serum creatinine levels. The patient was maintained on therapeutic heparin by continuous intravenous infusion. Two weeks after admission, pulmonary edema developed, for which she was treated and stabilized. A transesophageal echocardiogram revealed significant mitral stenosis with a mitral valve area <0.7 cm. It could not be determined whether this represented tissue overgrowth or a thrombus around the mitral valve. It was decided to proceed with open heart surgery and replacement of the mitral valve with the patient under fentanyl anesthesia. The fetal heart tones were continuously monitored. The left atrium was open longitudinally, and the mitral valve prosthesis revealed thrombotic aggregates occupying the left atrium, measuring 4.5 × 3.5 × 0.8 cm. The aortic valve prosthesis was inspected through a dental mirror introduced into the left ventricle and was thought to be normal. The mitral valve annulus measured only 27 mm; therefore a 27 mm St. Jude Medical prosthesis (St. Jude Medical, Inc., St. Paul, Minn.) was used. The prosthesis sat well in the annulus and all sutures were tied without difficulty. Unrestricted motion of both leaflets was carefully con-

firmed. The patient was weaned from cardiopulmonary bypass without difficulty.

One hour after the operation was begun, fetal heart rate decelerations (Fig. 1) were noted. Two minutes after the cardiopulmonary bypass pump was established at 33° C and high-flow–high-pressure perfusion, the fetal heart activity on the monitor was lost (Fig. 2) and fetal death was confirmed by ultrasonography. The cardiac surgery was completed without problems. The patient's postoperative course was unremarkable. Labor was induced with oxytocin 1 day after operation and a stillborn male fetus (640 gm) was delivered. Parents refused autopsy of the fetus. A tubal sterilization was performed 2 days post partum with the mother under general anesthesia.

Comment

Previous studies of fetal responses to cardiopulmonary bypass have found no relationship between gestational age and fetal mortality. Pregnant patients undergoing cardiopulmonary bypass have better fetal outcomes when high-flow–high-pressure normothermic perfusion is used. With this technique, fetal mortality and morbidity associated with the operation are considerably diminished. Maternal mortality has been reported up to 2%, whereas perinatal loss is approximately 10%.[1,2]

Fetal bradycardia during cardiopulmonary bypass has been observed consistently.[2] However, the fetal heart rate returns to baseline after discontinuation of cardiopulmonary bypass or an increase in blood flow from the pump. Our patient's clinical situation differs from that in patients in other studies in two ways. First, the fetus had intrauterine growth retardation, and second, the mother had severe preeclampsia. There are no reports on the effects of cardiopulmonary bypass on mothers with preeclampsia who have growth-retarded fetuses.

Clinical experience has demonstrated that antepartum fetal assessment can have a significant impact on the frequency of antenatal fetal deaths. In most high-risk pregnancies it is preferable to allow the fetus to remain in utero as long as possible. To decrease the likelihood of unnecessary premature interventions, tests of fetal well-being are used and delivery of a premature infant would be accomplished only if these tests suggest fetal compromise.

Delivery of an infant whose mother has mitral stenosis and pulmonary edema presents a serious problem. Hemodynamically, a defect exists that obstructs the left atrial outflow, which in turn decreases the cardiac output and elevates pressure in the left atrium and pulmonary vasculature. Distention of the left atrium with consequent decreased blood flow predisposes such patients to arrhythmias, such as atrial fibrillation, and to systemic thrombus formation. Cardiac output in pregnancy reaches its peak at approximately 30 weeks and is maintained until term. A patient with an already compromised left heart is at increased risk as pregnancy advances, increasing the incidence of heart failure and maternal mortality late in pregnancy and during the puerperium.

Open heart surgery with valve replacement should be considered in patients with heart failure who do not respond to medical treatment.[1,2] Options considered before operation for this patient included continuation of expectant fetal management as long as the mother tolerated the pregnancy well. This was done until the maternal heart failure was unremitting. The other option considered was to perform heart surgery and perform a cesarean section at the same time. This option was discarded because with the known perinatal mortality risk of 10%, the outcome for this fetus at 29 weeks was probably better if it remained undelivered.[1,2]

On the basis of our experience with this case, it would appear that a severely growth-retarded fetus with lack of uteroplacental reserve may better be delivered before the mother has cardiopulmonary bypass surgery since the likelihood of fetal survival during maternal cardiopulmonary bypass surgery appears to be remote. However, cardiopulmonary bypass may not have been the sole cause of fetal death. Coumadin treatment during the first trimester could have contributed to the result. Hall et al. have shown that such therapy may cause the fetal warfarin syndrome. In addition, the patient had severe preeclampsia and, as already described, the fetus was growth retarded. Because these findings are significantly different from those reported in previous studies, this case report supports the importance of the complete evaluation of pregnant patients with acquired heart disease during pregnancy.

Despite these factors it is our opinion that the use of cardiopulmonary bypass in pregnant patients with evidence of uteroplacental insufficiency is fraught with grave changes for the fetus. Thus it would seem reasonable in such situations to deliver the fetus before cardiopulmonary bypass is started.

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Laparoscopic diagnosis and treatment of interstitial ectopic pregnancy: A case report

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The laparoscope was used to diagnose and treat an interstitial pregnancy that had been overlooked on ultrasonographic examination. (Am J Obstet Gynecol 1990;163:587-8.)

Key words: Interstitial pregnancy, ectopic pregnancy, laparoscope

Interstitial implantation is one of the rarest sites of ectopic gestation. To our knowledge, this is the first published report of the laparoscopic treatment of an interstitial pregnancy.

Case report

The patient, a 25-year-old women, gravida 3, para 1, was first seen at the clinic with a 6-week history of amenorrhea and steady bleeding but without any pain. Initial assay result of β-subunit of human chorionic gonodotropin (β-hCG) was 4034 mIU/ml. Vaginal probe ultrasonography revealed an empty uterine cavity and a sonolucent area, 2.7 × 3.2 cm, with irregular borders in the right adnexa. She had no history of pelvic inflammatory disease. In 1981 she underwent a left salpingo-oophorectomy for removal of a fibrothecoma in the left ovary and a curettage in 1983 because of possible spontaneous, first-trimester abortion. In 1987 she underwent a curettage followed by a laparoscopic, right, linear salpingostomy for removal of a probable ectopic pregnancy.

The patient was admitted to the hospital 2 days after her clinic visit. The β-hCG level was 4400 mIU/ml; blood pressure, 114/80 mm Hg; pulse, 60 beats/min; temperature, normal; hematocrit, 39.1%; and hemoglobin, 12.9 gm/dl. The result of general physical examination was unremarkable. The abdomen was soft and distended with diffuse tenderness, and bowel sounds were absent. Pelvic examination disclosed evidence of bleeding; the cervix was long and closed, and the uterus was midplane, 6 to 8 weeks' size. No adnexal mass was palpated.

We performed a curettage that produced no tissue or placental villi. Because we suspected an ectopic pregnancy, we performed a diagnostic laparoscopy. Chromotubation, performed to identify a fistulous tract or to confirm patency, showed a nonpatent right tube and no dye spilling into the abdomen. Laparoscopic examination revealed multiple adhesions covering the left cornual portion of the uterus and a dilated area near the fimbriated end of the right tube suggestive of an ectopic pregnancy. This was removed by endocoagulation of the mesosalpinx and proximal end of the tube and sent for pathologic examination, the results of which were negative. Removal of the adhesions covering the left cornu revealed a 1 to 2 cm protrusion of the uterine wall that appeared to contain blue dye. After vasopressin solution was injected, a left cornual incision, 1 cm long, was performed to remove the products of conception, as confirmed by pathologic examination. Hemostasis was achieved by endocoagulation.

After the surgical procedure, we carefully examined the ultrasonogram and discovered a sonolucent area in the left cornual region that had been overlooked previously (Fig. 1).

Eight months after the operation, the patient has had no complications related to the procedure.

Comment

Although nontubal ectopic pregnancies represent <5% of all ectopic pregnancies, they account for approximately 20% of the fatalities attributed to ectopic gestations.[1] Difficulty in diagnosing these rare ectopic pregnancies may contribute to their high rate of complications.

The diagnosis of interstitial pregnancy is difficult because of the nonspecific symptoms. The most common symptoms, amenorrhea, pelvic pain, and bleeding, are similar to those encountered with other clinical conditions. In addition to history and physical examination, ultrasonography, and β-hCG assay, laparoscopy is of proved value in confirming the diagnosis of ectopic pregnancy. Laparoscopy, however, does have a 2% to 5% false-positive or false-negative rate. Early ultraso-

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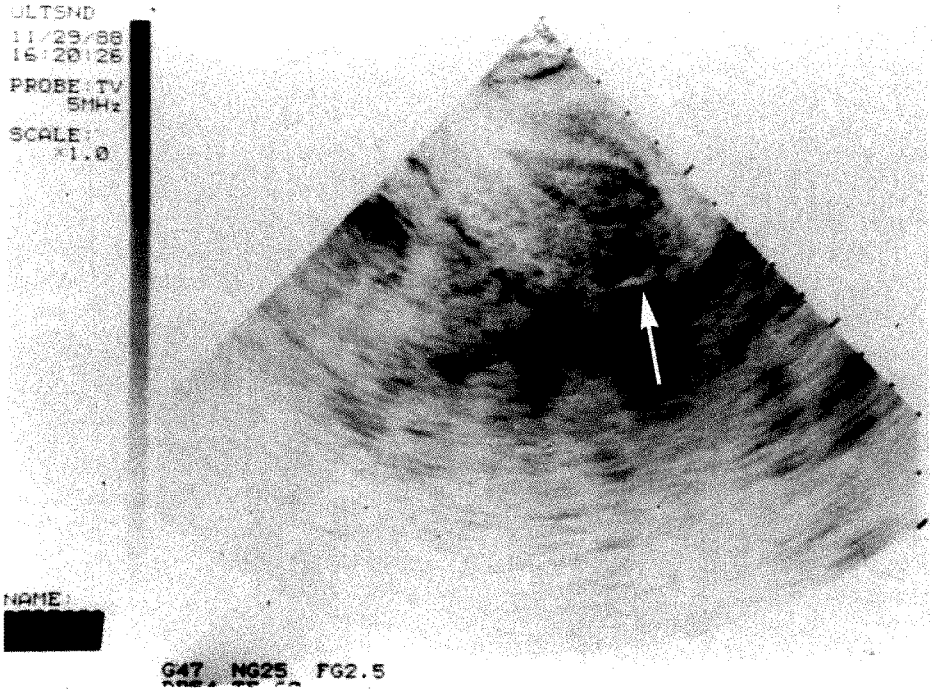


Fig. 1. Longitudinal view of uterus with vaginal probe ultrasonography. Note decidual cast of uterine cavity and interstitial pregnancy *(arrow)*.

nographic diagnosis of an interstitial pregnancy is quite difficult and, as happened in this case, the pregnancy can easily be overlooked.

In addition to its value as a diagnostic tool, laparoscopy coupled with pelviscopic surgical techniques can be used to treat ectopic pregnancy. We were able to use it to successfully treat an early, unruptured, interstitial pregnancy.

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A complete list of references is available from the authors on request.

A vesicovaginal fistula and intravesical foreign body

A rare case of the neglected pessary

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A case of neglected pessary is presented. After erosion through the anterior vaginal and bladder walls the device came to rest entirely within the bladder. Surgical management of removal of the pessary and repair of the resulting vesicovaginal fistula are described. Appropriate use of supportive pessaries as well as complications of misuse and neglect are discussed. (Am J Obstet Gynecol 1990;163:589-91.)

Key words: Pessary, vesicovaginal fistula, genital prolapse

A literature search that failed to produce a prior instance in which an entire intravaginal supportive device was found within the urinary bladder provoked this case report.

Case report

An 82-year-old white, multiparous woman complained of constant urinary leakage for 6 weeks. She had undergone a right nephrectomy after diagnosis of renal cell carcinoma 5 years previously and 29 months previously had been treated for cystocele by placement of an intravaginal supportive device. She had seen no physician since.

At pelvic examination urine was seen flowing from the vagina. The knob of a Gelhorn pessary could be felt and seen high in the posterior vagina. Gentle traction on the knob indicated marked impaction. Cystoscopy revealed the base of the device to be in the bladder. Cystography (Figs. 1 and 2) showed the device within the bladder and the vagina outlined by dye, implying the presence of a vesicovaginal fistula. At examination with the patient under anesthesia the device could no longer be felt in the vagina. Instead, it was felt through a 6 cm anterior vaginal wall defect to be in the bladder.

A suprapubic, extraperitoneal, transvesical approach through a low transverse incision was used to remove the foreign body, a Gelhorn pessary with a 2¾ inch base. A 6 cm vesicovaginal defect was observed to be 1 cm away from the left ureteral orifice. After passage of a feeding tube up to the left kidney, the fistula was circumcised at the junction of bladder mucosa and vaginal epithelium and the bladder was dissected free from the underlying vagina. The vaginal defect was closed with a single running suture and, after freshening the edges of bladder mucosa, the bladder defect was closed with figure-of-8 sutures. The cystotomy site was closed in two layers while the feeding tube, a cystotomy catheter, and a drain from the space of Retzius were exteriorized.

A cystogram performed 2 weeks after operation showed the bladder to be intact. There was no dye seen in the vagina, and the suprapubic tubes were removed. One month later the patient was voiding well and the vagina was well healed; there was no cystocele.

Comment

The elderly patient with genital prolapse has long been known to tolerate vaginal extirpative and reconstuctive surgery with minimal morbidity and mortality.[1] Nevertheless, supportive intravaginal devices (pessaries) continue to have a place in the management of such disorders.

The temporary use of a pessary during the period before definitive operation is strongly recommended. It enables the patient to enjoy a degree of comfort during the time required to undergo medical evaluation and to overcome medical complications in preparation for operation. In addition, it is not unusual for exteriorized vaginal epithelium to be atrophic, ulcerated, dehydrated, and of elephantoid consistency. A pessary provides internalization and allows time to treat the epithelium with estrogen so that tissues are better prepared at the time of operation.

A pessary may be used as definitive therapy for genital prolapse because of a patient's advanced age, medical complications that preclude surgical intervention, or commonly, the patient's refusal to undergo surgery.

Whether used as a temporary or definitive measure, a misused or neglected pessary is dangerous. Common complications include severe ulceration of the vagina and incarceration that necessitate the use of general anesthesia for removal of the device. In the past we

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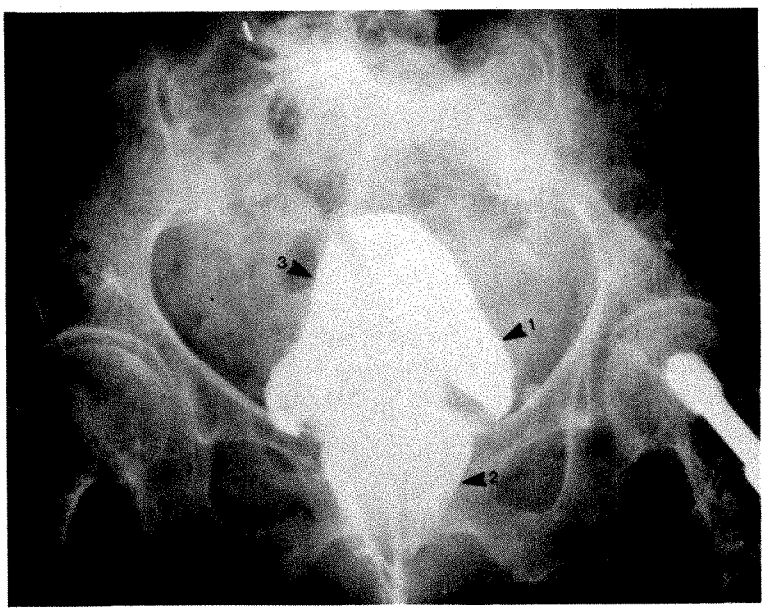


Fig. 1. Cystogram (anteroposterior view).

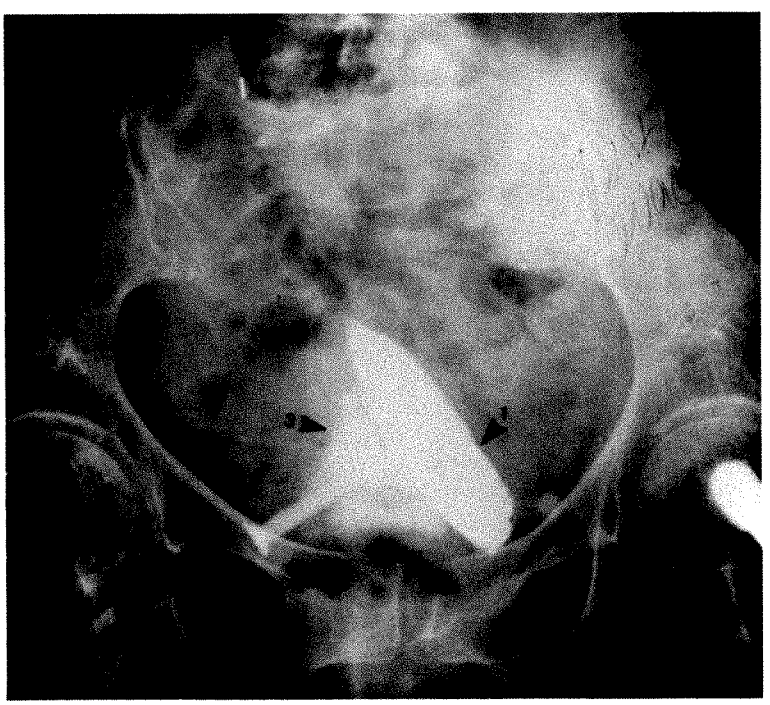


Fig. 2. Postevacuation cystogram. *1*, Gelhorn pessary within bladder; *2*, dye in vagina; *3*, dye in bladder.

have seen both a rectovaginal fistula and a vesicovaginal fistula in association with pessary misuse or neglect and are aware of a report in which an ulcerating pessary caused simultaneous rectovaginal and vesicovaginal fistulas.[2] To avoid misuse of a pessary the clinician must make certain that the patient and her family or her institutional support staff understand the importance of frequent, periodic examinations during which the device is to be removed, the vagina cleansed, and the vaginal epithelium inspected for evidence of pressure trauma. Unfortunately, such patients are likely to be elderly, forgetful, physically separated from family,

or institutionalized. Patient neglect then supersedes proper treatment and the device is all but forgotten, with a resulting complication as occurred in our case.

When the pessary in our patient was removed, the question arose as to whether closure of such a large vesicovaginal fistula should be done immediately or postponed to allow involution of the lesion with subsequent transvaginal repair. Our concern was that failure of the transvesical repair might result in a lesion larger than the original with encroachment on the sole remaining ureter. In addition, one of us (M. L. T.) has resorted previously to an abdominal approach in only four of 140 patients with a variety of vesicovaginal fistulas, so that a transvaginal approach seemed reasonable. Our decision for immediate repair was made based on the fact that when viewed transvesically, the fistula borders appeared neither macerated nor infected and the stented left ureteral orifice was clearly in view.

In summary, a rare complication of the neglected pessary and the management of that complication are reported. The results of misuse and neglect of pessaries are stated, and the appropriate use of a pessary is described. The reasons for immediate repair of the complicating vesicovaginal fistula are discussed.

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Malignant leiomyomatosis peritonealis disseminata

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Leiomyomatosis peritonealis disseminata is a rare condition characterized by the presence of multiple intraabdominal nodules that consist of benign smooth muscle. We found 42 documented cases in the literature. Malignant degeneration appears to be extremely rare. We describe the second case with proved malignancy. (Am J Obstet Gynecol 1990;163:591-3.)

Key words: Leiomyomatosis, leiomyosarcoma, peritoneum

Leiomyomatosis peritonealis disseminata is a rare condition. A search of the literature revealed only 42 documented cases. In one case malignant degeneration occurred. This report presents the second case of malignant leiomyomatosis peritonealis disseminata.

Case report

A 25-year-old, white nulligravid woman was referred because of acute right lower abdominal pain. She did not have nausea, vomiting, or abnormal weight loss. She had regular menstrual periods without the use of oral contraceptives. Appendectomy had been performed 2 years previously. The right lower abdominal quadrant was tender on palpation. Gynecologic examination revealed a normal-sized uterus with an anterior solid nodule and a tender, only slightly mobile mass on the right side. Both tumors had an estimated diameter of approximately 7 cm. General blood and urinalysis gave unremarkable results, except for an erythrocyte sedimentation rate of 22 mm in the first hour. Ultrasonographic examination revealed a pelvic tumor with solid and cystic parts on the right side, but not attached to the uterus. The anterior wall of the uterine corpus showed a small solid nodule. Laparotomy was performed after induction of general anesthesia, and two nodular tumors were found to be present, each with a diameter of approximately 6 cm. One tumor was attached to the ascending colon, and the other tumor was situated on the anterior surface of the uterine corpus. The omentum, colon, and small intestine were scattered with firm, gray-white subperitoneal nodules, varying in size between a few millimeters to 2 cm. The ovaries showed no abnormalities. Microscopic examination of frozen biopsy specimens revealed clusters of spindle-shaped smooth muscle cells, without histologic features of malignancy. The two large tumors

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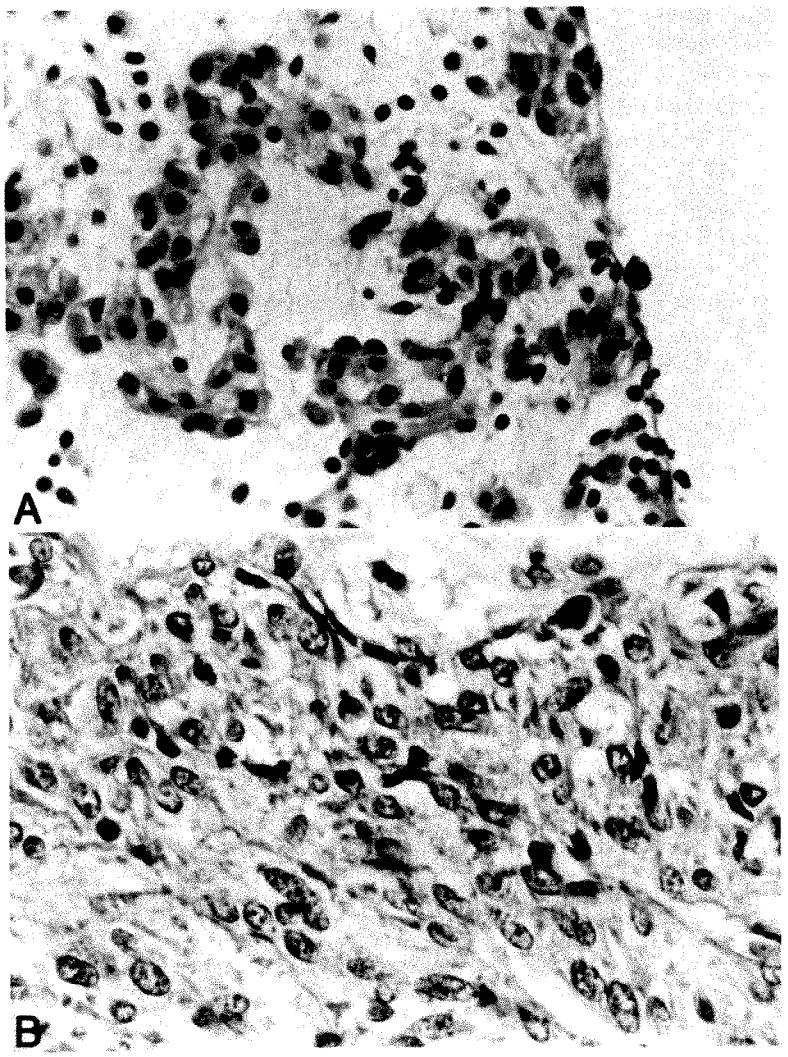


Fig. 1. A, Diagnosed as leiomyomatosis peritonealis disseminata. (Hematoxylin and eosin stain; original magnification ×480.) **B,** Sarcomatous degeneration 1 year later. (Masson trichrome stain; original magnification ×480.)

were removed and the uterus and ovaries were left behind. Histologic examination of the tumors showed fusiform smooth muscle cells, without abnormal mitotic activity or atypical nuclei, in decidualized connective tissue. A diagnosis of leiomyomatosis peritonealis disseminata was made (Fig. 1, *A*).

Six months later the patient had no complaints. Gynecologic examination revealed no abnormalities. On laparoscopic inspection no change in the size or number of the nodules was apparent. Biopsy specimens were taken from some of the nodules, which on histologic examination showed the same features as those observed in the tumors removed earlier. One year after laparotomy, the patient was seen at follow-up examination without any clinical signs or symptoms. However, a solid tumor of approximately 10 cm diameter was felt in the right lower abdominal quadrant, and vaginal and rectal palpation revealed a firm mass in the cul-de-sac. A second laparotomy was performed and multiple tumors varying in size from 0.5 to 10 cm were found scattered throughout the abdominal cavity. The uterus and ovaries were covered in dense adhesions. Nodules were felt on the dome of the liver.

Histologic examination of biopsy specimens showed marked cellularity and numerous mitoses. A diagnosis of poorly differentiated leiomyosarcoma was made (Fig. 1, *B*), and it was decided to refrain from further attempts to surgically remove the tumors. The patient refused chemotherapy and was treated with a luteinizing hormone–releasing hormone agonist. The abdominal tumors increased in size and the patient's condition progressively deteriorated. She died 22 months after the initial diagnosis of leiomyomatosis peritonealis disseminata; autopsy was refused.

Comment

Leiomyomatosis peritonealis disseminata is a rare disorder of unknown cause. We found 41 documented cases in the literature since the first case was reported

in 1952.[1] Patients with leiomyomatosis peritonealis disseminata are exclusively female. The average age at the time of diagnosis is 37 years (22 to 55 years). In one reported case leiomyomatosis peritonealis disseminata was found at autopsy in a 69-year-old woman. There seems to be a predisposition for blacks (50% of those whose race was reported). Symptoms of lower abdominal pain and menorrhagia occurred, but patients were often asymptomatic, in which case the diagnosis was made at cesarean section (nine patients), laparotomy for other reasons (eight patients), or laparoscopic tubal ligation (two patients). At laparotomy the macroscopic findings may simulate malignancy.

Multiple subperitoneal gray-white masses with a firm to rubbery consistency, varying in size from 0.1 to 10 cm were found on the parietal peritoneum, uterus, omentum, and the mesentery in all patients. On microscopic examination the lesions appear to consist of subperitoneal smooth muscle proliferations. In contrast to leiomyosarcoma there is little mitotic activity.[1] In some cases a decidual reaction, fibroblasts, and myofibroblasts were found in the nodules. Because of this it has been suggested that leiomyomatosis peritonealis disseminata is a fibrotic reaction to deciduosis rather than smooth muscle proliferation.[1]

The pathogenesis of leiomyomatosis peritonealis disseminata is unknown, but a hormonal factor may be involved. More than half the reported patients were pregnant or taking oral contraceptives at the time of diagnosis. Disseminated leiomyomatosis has been induced in animals by means of administration of estrogens, and regression occurred after cessation of the stimulation.

Regression of the tumors has also been described after surgical castration, withdrawal of oral contraceptives, and post partum. A search of the literature revealed a single report of malignant degeneration in leiomyomatosis peritonealis disseminata. In an apparently healthy 27-year-old gravida 1 woman, leiomyomatosis peritonealis disseminata was found at cesarean section. Six months later the patient was seen with a rapidly growing pelvic tumor and diffuse bone metastases. Hysterectomy, salpingo-oophorectomy, and resection of most of the pelvic tumors were performed. Pathologic findings were characteristic of small spindle cell sarcoma. Despite combination chemotherapy the patient died within 2 years after the laparotomy.[2]

Leiomyomatosis peritonealis disseminata appears to be a rare condition that usually runs a benign course. There are no firm guidelines in the literature with regard to the management of these patients. Although we report the second documented case of malignant degeneration, we believe that an aggressive approach to leiomyomatosis peritonealis disseminata is not warranted.

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An abdominal pregnancy 10 years after treatment for pelvic tuberculosis

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An abdominal pregnacy after treatment for female genital tuberculosis is presented. Early treatment after the diagnosis of female genital tuberculosis may restore fertility in the rare patient. Chemotherapy is the cornerstone of therapy. Ectopic pregnancies are common and should be ruled out to avoid catastrophic results. (Am J Obstet Gynecol 1990;163:594-5.)

Key words: Pelvic tuberculosis, abdominal pregnancy

Intrauterine pregnancy is rare after genital tuberculosis. It may occur occasionally if the disease is diagnosed and treated in its very early stage. Ectopic pregnancies have been reported after antituberculous therapy and after reconstructive surgery for occlusions of the oviducts because of this condition.[1] An abdominal pregnancy after treatment for female genital tuberculosis is presented and discussed.

Case report

A 38-year-old woman who had been infertile for 10 years reported to the emergency department complaining of abdominal pain, nausea, and vomiting. She stated that she was 13 weeks pregnant according to her last menstrual period. The result of a urine pregnancy test was positive, and the patient complained of lower abdominal pain and vaginal bleeding for the past week.

During an infertility workup 8 years ago hysterosalpingography revealed a bilateral tubal block and signs compatible with female genital tuberculosis. Biopsy from the endometrium was reported as granulomatous endometritis. She received multiple-agent antituberculous therapy (isoniazid 300 mg/day; ethambutol 1000 mg/day; and rifampin 600 mg/day) for 12 months.

Physical examination disclosed an abdomen that was mildly distended with rebound tenderness in lower quadrants. A left-sided tender mass was palpated bimanually.

Ultrasonographic examination of the pelvis revealed an empty uterus and a gestational sac occupied by a 13-week embryo with positive cardiac activity adjacent to the uterus in the pouch of Douglas (Fig. 1). A presumptive evidence of ovarian or abdominal pregnancy was made.

At laparotomy it was seen that the sac and the embryo measuring 12 × 10 × 10 cm occupied the pouch of Douglas with the placenta attached to the posterior leaf of the broad ligament and partially to the Douglas peritoneum. The placenta was partially separated and there was approximately 300 ml of blood filling the Douglas pouch. The tubes were intact with no evidence of uteroperitoneal fistula, and the ovaries on both sides were normal with a leaking corpus luteum occupying the left ovary. A left salpingo-oophorectomy was performed, removing the placenta totally with partial dissection of the Douglas peritoneum; the bleeding sites were cauterized.

The pathologic examination revealed a normal tube with calcifications in the muscularis layer. There were no chorial elements in the ovary and the sac showed no evidence of ovarian tissue. A diagnosis of abdominal pregnancy was made.

Comment

Primary abdominal pregnancy is rare and represents 1.6% of all ectopic pregnancies. Criteria first set by Studdiford should be met to make the diagnosis.[2] The outcome of pregnancy is usually fetal death or placental separation with intraperitoneal bleeding. Ultrasonography is useful in diagnosis of the condition, especially if the uterus is empty and both ovaries are visible. Recurrent abdominal pain in an infertile woman should alert the clinician to the probability of abdominal pregnancy in addition to more likely diagnoses, such as recurrent pelvic inflammatory disease, including female genital tuberculosis, tubal ectopic pregnancy, and threatened abortion. Prompt termination is necessary once the diagnosis is made.

Female genital tuberculosis should be treated medically after the diagnosis. Operation should not be the

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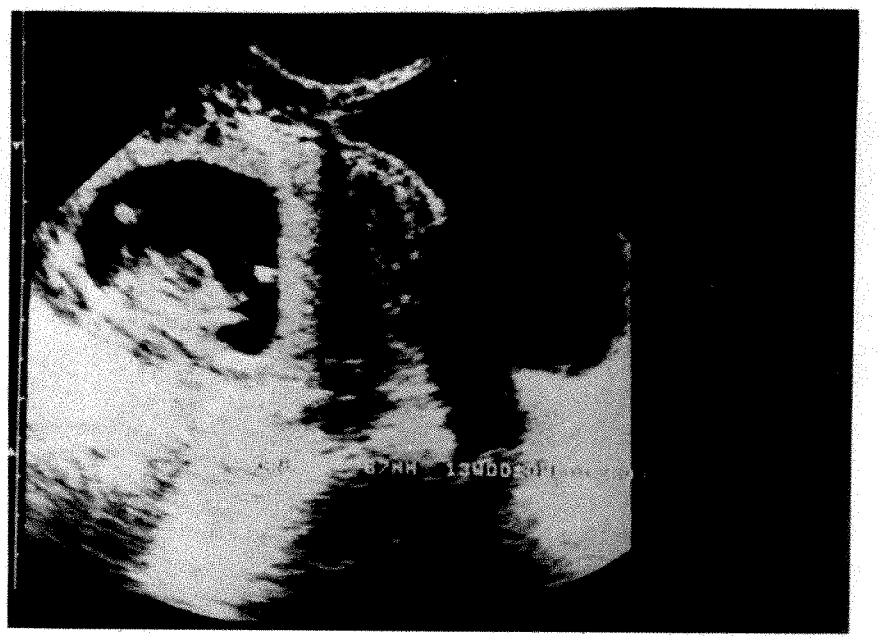


Fig. 1. Pelvic ultrasonogram of the patient reveals an empty uterus and a gestational sac localized in the pouch of Douglas.

initial mode of therapy because of the possibility of activating latent disease; however, if use of the antituberculous drugs are not successful and symptoms or tuboovarian masses remain after 1 year, operation should be considered with use of an additional drug not used in initial treatment. Hysterosalpingogram can be diagnostic if the typical signs are seen. Endometrium is involved in 50% of cases. Early diagnosis and therapy may restore fertility, although ectopic pregnancies and abortions are more common than successful intrauterine pregnancies. In a 31-year study of 1436 cases of female genital tuberculosis, only four pregnancies (two localized ectopically to the tubes) have been reported.[1]

A patient with a history of female genital tuberculosis should be followed up indefinitely. Their pregnancies should be considered high risk, and ectopic nidation, which may occur even after a long period, should be ruled out to avoid catastrophic results.

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Papillary cystadenoma of the broad ligament in von Hippel-Lindau disease

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We present radiologic-pathologic correlation in a case of von Hippel-Lindau disease diagnosed on the basis of the discovery of papillary cystadenoma of wolffian duct origin, a rare calcified tumor of the broad ligament that was visible on the abdominal radiograph. (AM J OBSTET GYNECOL 1990;163:596-8.)

Key words: Cystadenoma, broad ligament, von Hippel-Lindau disease, inherited diseases

von Hippel-Lindau disease is a potentially fatal disorder with an autosomal dominant pattern of inheritance. We report a case in which the first clinical manifestation of this disease was a distinctive rare bilateral tumor of the broad ligament.

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Case report

A 35-year-old, asymptomatic, white woman was evaluated for right lower-quadrant abdominal pain. On pelvic examination the right ovary was slightly enlarged. Neurologic examination and routine laboratory tests, including urinalysis, were normal. A radiograph of the abdomen revealed a curvilinear calcification in the right pelvis (Fig. 1). Ultrasonography demonstrated a sonolucent mass containing an echogenic region in the right adnexa. At operation the fallopian tubes and bilateral paratubal masses were excised. Pathologic examination revealed a 5 cm bilobed, cystic right paratubal mass with focal calcification of its wall. Dissection of the mass disclosed two locules, 3.2 and 2 cm, con-



Fig. 1. Detail from abdominal radiograph demonstrates crescentic calcification in the pelvis *(arrows)*. Differential diagnosis includes dermoid cyst and mucinous cystic tumor.

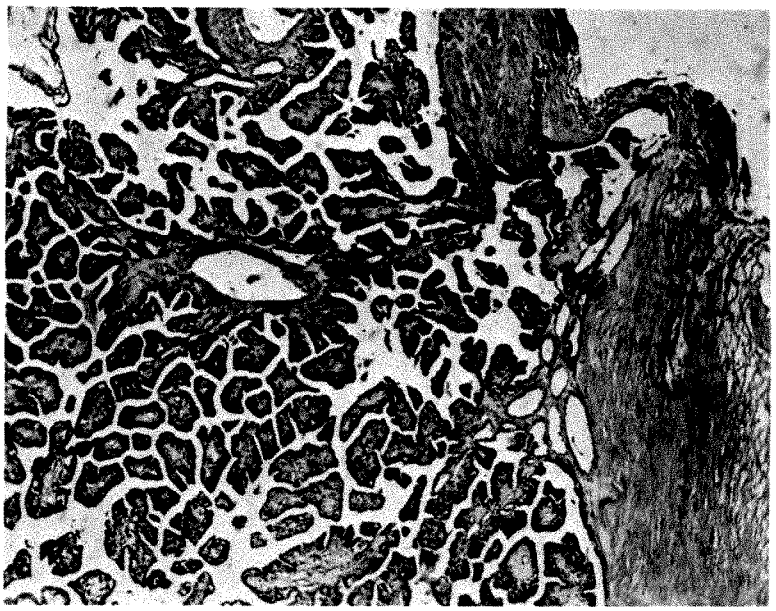


Fig. 2. Papillary cystadenoma consisting of small papillae lined by cuboidal epithelial cells. The wall of the cyst is thickened and hyalinized. (Original magnification × 125.)

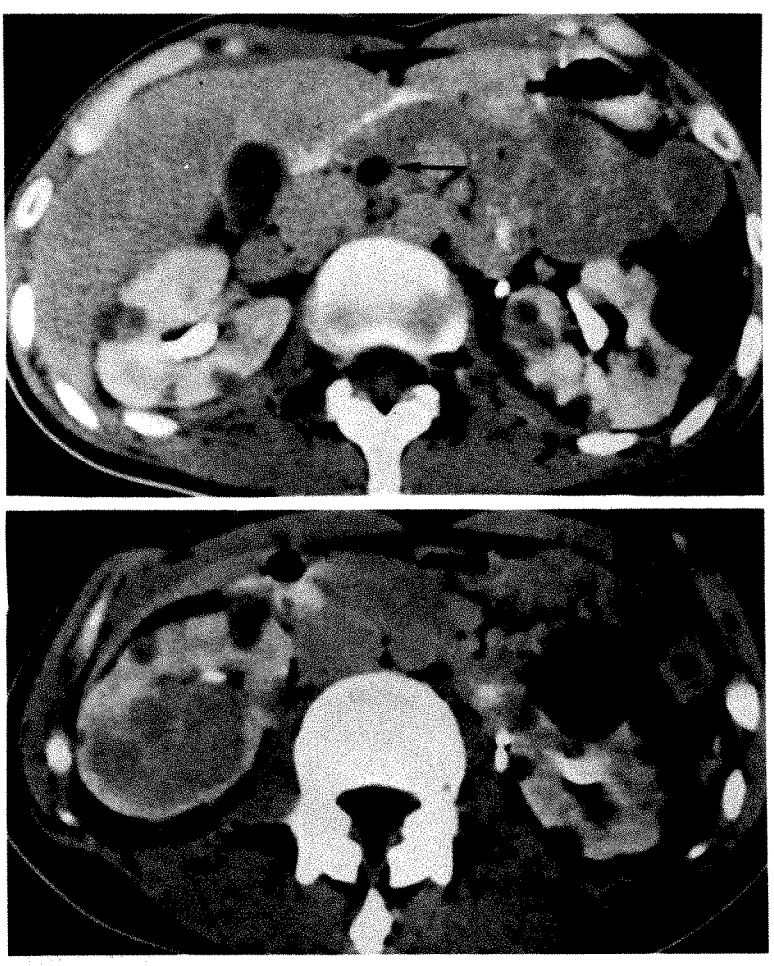


Fig. 3. Axial computed tomography of the abdomen demonstrates numerous cystic and solid lesions in the kidneys and a small pancreatic cyst *(arrow)*.

taining polypoid structures with papillary surfaces. The left paratubal mass was a 2 cm unilocular cyst otherwise similar to the right-sided mass.

Microscopic examination revealed that the cysts contained polypoid masses characterized by an intricate network of spaces with a complex papillary pattern (Fig. 2). The cores of the papillae were composed of cellular to hyalinized to edematous connective tissue. The papillae were lined by bland-appearing cuboidal epithelial cells with central nuclei. The cytoplasm was densely eosinophilic or showed surface vacuolizaton; no cilia were observed. The walls of the cysts were composed of fibrous tissue with patchy hyalinization and focal calcification on the right side. The fallopian tubes appeared normal. A diagnosis of papillary cystadenoma of wolffian duct origin, highly suggestive of von Hippel-Lindau disease, was made.

Ophthamologic examination was normal. Computed tomography of the brain demonstrated three homogeneously enhancing cerebellar lesions consistent with hemangioblastomas. Computed tomography of the abdomen revealed bilateral renal solid and cytic masses and a small pancreatic cyst (Fig. 3). Bilateral partial nephrectomies were performed with the removal of multiple renal cell carcinomas.

Comment

The findings associated with von Hippel-Lindau disease include hemangioblastomas, retinal angiomas, renal cell carcinomas, renal, pancreatic, hepatic, and splenic cysts, pheochromocytomas, and less commonly, adenomas of the liver, pancreas, epididymis, and kidneys.

In men, papillary cystadenoma of the epididymis is an uncommon tumor that is considered almost diagnostic of von Hippel-Lindau disease when bilateral. It occurs in 10% of men with the disease.[1] A histologically identical tumor in women is the papillary cystadenoma of the broad ligament of wolffian duct origin,[1] only three of which have been reported. One was bilateral and the other two apparently unilateral; each was associated with von Hippel-Lindau disease.[1,2] Radiologic findings were described in one case and included curvilinear calcifications in an adnexal mass on computed tomography. In none of the cases was this tumor the first clinical manifestation of the disease; in two cases, von Hippel-Lindau disease had been evident for 20 or more years before presentation of the paraovarian mass.

The classic lesions of von Hippel-Lindau disease were clinically silent in this case. The detection of a cystic calcified pelvic mass led to the diagnosis of von Hippel-Lindau disease. This expedited the detection of renal and cerebellar tumors, allowing the performance of a kidney-sparing operation and close monitoring of the cerebellar lesions. In addition, screening of the patient's family will hasten the diagnosis of any additional cases of this potentially fatal illness.

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Anencephalics as organ donors

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Anencephalics can be divided into a large group without a functional hypothalamohypophysial system and a smaller group with a functional hypothalamohypophysial system. Anencephalics of the first group do not live more than a few hours, whereas the anencephalics of the second group can live up to 3 days. Those with a functional hypothalamohypophysial system have shown pain reaction. In anencephalics without a functional hypothalamohypophysial system, the endocrine pancreas does not reach full maturation and the use of these glands for islet transplantation can be questioned. (Am J Obstet Gynecol 1990;163:599-600.)

Key words: Anencephaly, transplantation, endocrine pancreas

The use of anencephalic newborns as organ donors is currently of interest.[1] An important ethical question remains regarding at what time after birth organs can be used, without damage of these organs. Although we do not as yet have any personal practical experience in transplantation from such donors, it is important to relate our data on these cases collected 20 years ago in northern Ireland. The main purpose was the study of the fetal endocrine pancreas.[2] In nearly all cases diagnosis of anencephaly was made before birth; induction of labor was performed by rupture of the membranes associated with oxytocin infusion. In resistant situations hypertonic saline solution was injected into the amniotic fluid.

Because we needed fresh material only anencephalics who were born alive were used. An autopsy was performed after death was confirmed by a pediatrician of the local hospital. In connection with our experimental design only anencephalics born after 30 weeks' gestation were used. The results of our previous studies[2] had clearly demonstrated that a functional hypothalamohypophysial system was necessary for complete morphologic and functional maturation of the fetal endocrine pancreas.

Changes as seen in newborns of mothers with diabetes were only present in anencephalics with a functional hypothalamohypophysial system. Islet hypertrophy, B cell hyperplasia, and hyperinsulinism were not found in anencephalics without a functional hypothalamohypophysial system born to a mother with diabetes.[2] We collected data on 33 cases. The criteria for the presence of a functional hypothalamohypophysial system were as follows: (1) the macroscopic presence of a hypothalamohypophysial structure, (2) the presence of a fetal adrenal cortex by microscopic examination, and (3) a normal estrogen level in a maternal urine sample. Twenty-six cases were classified without a functional hypothalamohypophysial system and seven had a functional hypothalamohypophysial system.

Birth weight was increased only in anencephalics with a functional hypothalamohypophysial system born to a mother with diabetes. The birth weight of anencephalics without a functional hypothalamohypophysial system was between the 10th and 25th percentiles. Polyhydramnios (more than 2 L of fluid) was present in 24 of 26 cases without a functional hypothalamohypophysial system and in only one of seven anencephalics with a functional HH system (the mother had diabetes). We suggested at that time that only anencephalics with a functional hypothalamohypophysial system are capable of swallowing. Because we did make some clinical observations of these cases, information is available on the natural history of anencephaly after birth. The Apgar score 5 minutes after birth was always <4 in anencephalics without a functional hypothalamohypophysial system, except in one case the Apgar score was >4 in an anencephalic with a functional hypothalamohypophysial system.

The anencephalics did not receive any intensive treatment. Of the 26 cases without a functional hypothalamohypophysial system, 12 newborns died within 1 hour, 7 died the next hour, and all died within 4 hours. Of the seven cases with a functional hypothalamohypophysial system, one newborn died within 4 hours, a second died within 24 hours, two died the second day, and three died the third day.

It seems that anencephalics are certainly not a ho-

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mogeneous group with regard to transplantation; furthermore we thought that such cases with a functional hypothalamohypophysial system did have pain reactions. In addition, endocrine disorders are present in such newborns. These changes may be of importance concerning the functional capacity of the donated organ. Certainly in anencephalics without a functional hypothalamohypophysial system the endocrine pancreas does not reach full maturation, which can cause problems when these glands are used for islet transplantation.

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Study of internal structure of the human fetus in utero by echo-planar magnetic resonance imaging

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The ultrafast echo-planar magnetic resonance imaging technology, developed and built in Nottingham, has been used to produce the first snapshot images of the human fetus in utero. The imager, operating at a proton resonance frequency of 22 MHz, produces transaxial views in 64 or 128 milliseconds. These images comprise either 64 × 128 or 128 × 128 pixels with an in-plane resolution of 3 × 3 mm^2. The slice thickness is 10 mm. Fetal scans of up to 32 contiguous slices are produced in a few minutes. These have been used to study the internal structure of the uterus and the fetus in a range of cases with gestations ranging from 26 weeks to term. Echo-planar imaging seems particularly suitable as an imaging modality since its high speed obviates image blurring arising from fetal motion. (AM J OBSTET GYNECOL 1990;163:601-7.)

Key words: Echo-planar imaging, snapshot magnetic resonance imaging, fetal scans in utero

Echo-planar imaging[1, 2] is a particular form of magnetic resonance imaging in which complete snapshot images are obtained in ≤128 milliseconds. It evolved from the principles of magnetic resonance imaging introduced by Mansfield and Grannell[3] in 1973. In this article is presented a series of images obtained from the human fetus in utero during the second and third trimesters of pregnancy with the echo-planar imaging technique. These pictures have been obtained from the first pregnant patients who underwent imaging with a unique home-built magnetic resonance machine. Preliminary reports of this work are given elsewhere.[4-7]

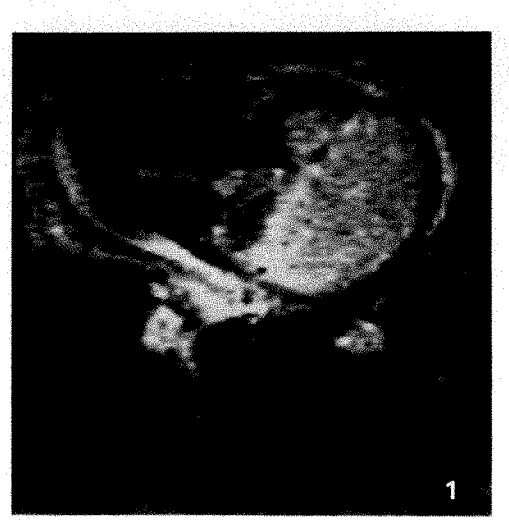
Methods and patients

All images were obtained with a 0.5 T superconductive magnet with the modulus-blipped echo-planar single-pulse technique,[8-11] a variant of the original echo-planar technique.[1] Full details of the application of this technique to imaging pregnant patients are described elsewhere.[12] Two-dimensional images were obtained in either 64 or 128 milliseconds after a single excitation of the spin system. A modulus Fourier transformation converted the raw data into the final magnetic resonance image. Resolution varied between 1.5 and 3 mm. In ultra-high-speed echo-planar imaging complete echo-planar images may be acquired, formed, and displayed in real time at up to 20 frames per second.[10] In the present work frame rates of 1 or 2 per second were used. Sixteen patients have had imaging done with this technique, at gestations varying from 21 weeks to term. All of the fetuses imaged so far have been from pregnancies deemed to be abnormal, with congenital abnormalities previously diagnosed on ultrasonography, suspected intrauterine growth retardation, or problems with the placental site. Fully informed and written consent was obtained from all patients. Permission for imaging of patients in the second and third trimesters of pregnancy in Nottingham has been obtained from the local committee on ethics. The imaging conditions used in this study were all well within the safety guidelines recommended by the National Radiological Protection Board.

Results

Fig. 1, *1*, shows a transverse section through the pelvis of a woman who was 38 weeks pregnant. The maternal spine is at the bottom of the picture and an oblique coronal section is shown through the fetal skull and brain. The slice is 10 mm thick. The fetus is outlined by a rim of white amniotic fluid. The bone of the fetal

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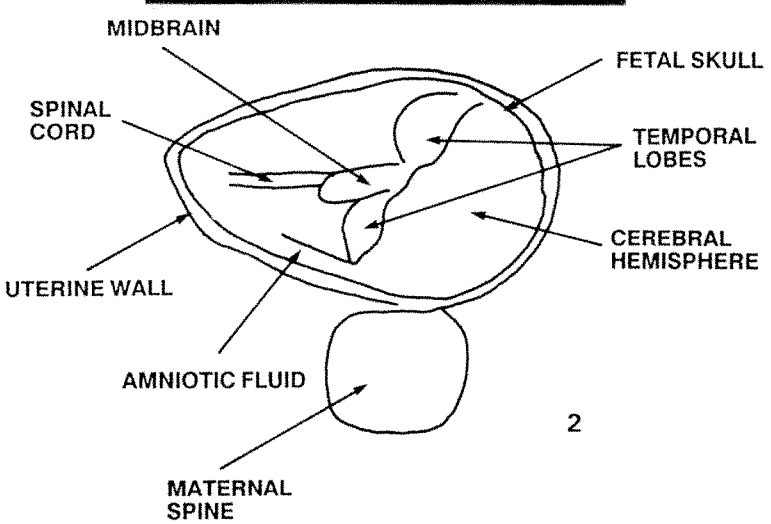


Fig. 1. 1, Echo-planar transectional snapshot through a 38-week fetal head. Image exposure time 128 milliseconds. Slice thickness 10 mm. In-plane resolution 3 × 3 mm^2 (13101). **2,** Annotated sketch showing salient features of **1**.

skull appears dark because of its low signal, but within this can be seen the fetal brain, which is homogeneous because of its lack of myelination. The cerebral hemispheres appear laterally on the right side of the uterus with the temporal lobes seen anteriorly and posteriorly in the midline. The midbrain, lower brain stem, and upper spinal cord are seen running away obliquely. The pons is shown particularly clearly. Fig. 1, *2*, is a sketch with salient features annotated.

Fig. 2, *1*, shows a transverse section through the pelvis of a pregnant patient at 40 weeks' gestation. The maternal spine, with a high signal from the cerebrospinal fluid, is shown in the lower part of the picture. The uterus and its contents occupy the upper part of the picture. The amniotic fluid has a high water content and consequently a high signal while an intermediate signal is seen from the rim of placenta lining the posterior aspect of the uterus. The fetus is facing to the right. A transverse section through part of the fetal brain is shown enclosed within the low signal of the fetal skull (see annotated sketch of Fig. 2, *2*). The cerebral hemispheres, the temporal lobes, and the brain stem can be seen clearly.

Fig. 3, *1* through *5*, shows five transverse images taken at intervals through the fetal chest in a 37-week pregnancy. The placenta is on the right lateral, posterior aspect. The fetus is on the left anterolateral aspect facing the placenta (see annotated sketch, Fig. 3, *6*). In each of the pictures the fetal spinal canal can be seen in the left anteriolateral aspect of the uterus and appears as a high signal representing the cerebrospinal fluid in the spinal canal. A dark circle anterior

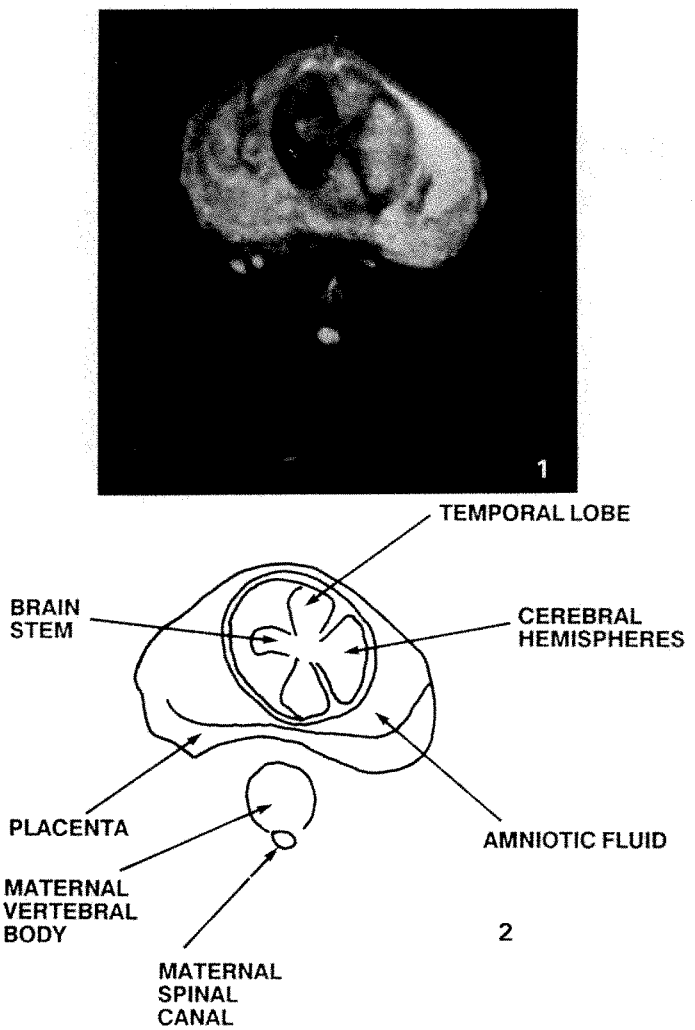


Fig. 2. 1, Transaxial snapshot image through uterus at 40 weeks' gestation. The imaging plane is through the fetal cerebral hemispheres. Imaging time 128 milliseconds. In-plane resolution 3 × 3 mm^2 (15501). **2,** Annotated sketch of **1** above, indicating major morphologic detail.

to it within the fetus, represents the fetal vertebral body. Within the fetus the lungs lie anteriorly to the spinal canal and vertebral body and on either side of the midline. The lungs appear as high-signal areas, because of the fluid that they contain, fanning out from the hilum to the periphery on each side. This series of pictures shows the lung fields from the lung apexes (Fig. 3, *1*), enlarging as slices are taken serially through the chest, until they disappear at the level of the diaphragm in Fig. 3, *5*. It is clear that when contiguous slices with a given thickness (10 mm) are taken through the fetal chest the fetal lung volumes can be measured. In some of the images, particularly Fig. 3, *4*, the internal structure representing the blood vessels is seen within the lung fields. The heart lies anteriorly in the fetus between the two lung fields, but the interal structure of this organ is not seen particularly well in this series of images. In Fig. 3, *5*, the transverse slice is taken through the diaphragm and part of the upper abdomen. The area of high signal in the left of the fetus represents the uppermost part of the stomach. In Fig. 3, *3*, *4*, and *5*, the placenta is particularly well seen on the right lateral aspect of the uterus; considerable heterogeneity is seen, with the dark circular areas representing blood flow within this organ.

Fig. 4 shows two pictures of a series obtained from a 26-week fetus. The fetal heart is depicted in the middle of each picture with the lung fields to either side. In Fig. 4, *1*, the fetus is facing the maternal spine and all four cavities of the heart are shown as low-signal areas. The walls of the heart can be seen clearly, as can the intraventricular septum. The atria and ventricles

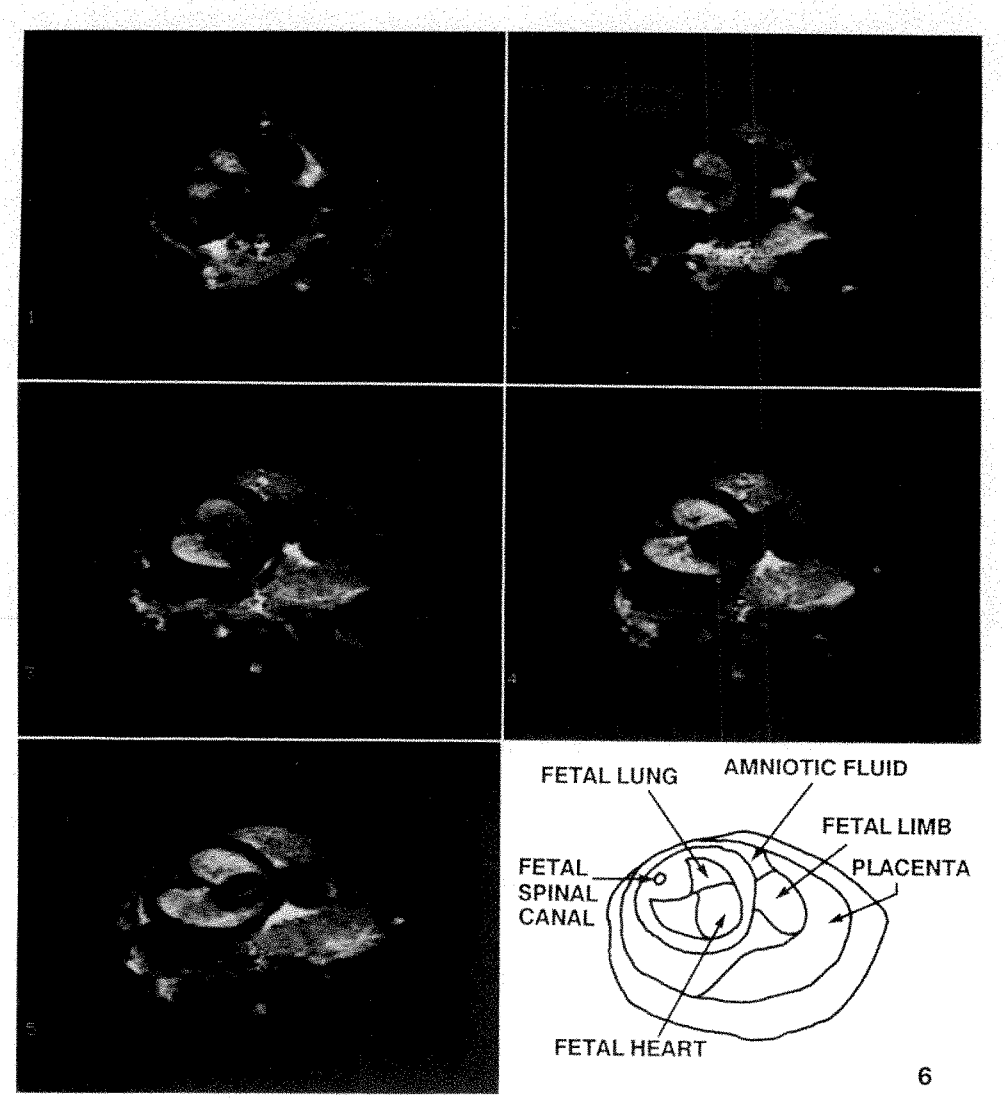


Fig. 3. 1 to **5,** Five contiguous transections through a fetal chest at 37 weeks' gestation. Snapshot exposure time 64 milliseconds. In-plane resolution 3 × 3 mm² (13201). **6,** Diagram illustrating main morphologic details of images **1** through **5**.

are demonstrated and the tricuspid and mitral valves can be distinguished. The low-signal areas in all four chambers are caused by the movement of the blood. For example, in Fig. 4, *2*, taken at a different stage of the cardiac cycle, although blood is still moving rapidly in the ventricles in systole, the flow is clearly more sluggish in the atria, yielding a high-signal intensity.

Fig. 5 shows three transverse slices taken through the abdomen of a fetus within the uterus of a patient who was 36 weeks pregnant. The maternal spine lies at the bottom of the picture with the uterus occupying the upper portion of each picture. The placenta lies laterally on the left with the fetus shown anterolaterally on the right facing the placenta. Considerable heterogeneity can be seen representing blood flow within the placenta on each of the pictures. The placental and fetal boundaries are outlined by the starkly white high signal of the amniotic fluid. The fetal abdomen is outlined by a low-signal ring that mainly represents subcutaneous fat. This has been deliberately suppressed by chemical selection of the water signal only.[13] In Fig. 5, *1*, the fetal spinal canal can be seen as a high-signal area posteriorly within the fetus. The vertebral body is a low-signal circular area immediately anterior to the canal, with the aorta and inferior vena cava immediately anterior to it. To either side of these vessels and the vertebral body, the upper part of the kidneys can be seen. The anterior part of the fetal abdomen is mainly occupied by the fetal liver, although some fluid can be seen in the first part of the duodenum, illustrated by the high-signal area. A loop of cord is seen within the amniotic fluid. In Fig. 5, *2*, the slice is taken

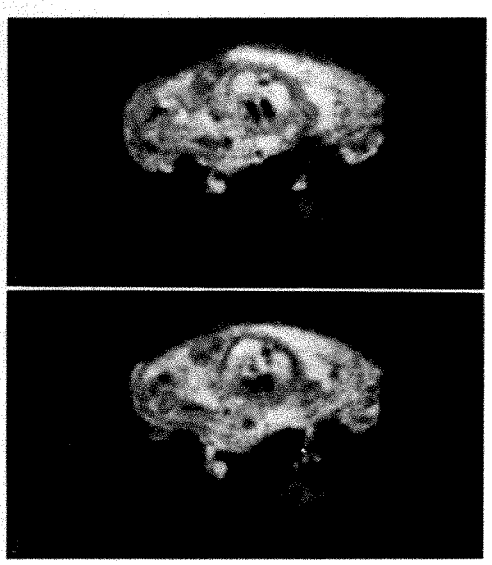


Fig. 4. Snapshot echo-planar imaging transections through mediastinum of fetus at 26 weeks' gestation. **1,** Four-chamber view through heart (dark region) in atrial and ventricular systole. **2,** Later in atrial diastole and ventricular systole. Atria appear bright because of slow flow, whereas ventricles appear dark because of high blood velocity. Imaging time 64 milliseconds. In-plane resolution 3 × 3 mm^2 (13001).



Fig. 5. Three snapshot echo-planar imaging transections at different levels in fetal abdomen. **1,** Fetal liver, **2,** Fetal kidneys. **3,** Fetal bowel and thighs. Imaging time 128 milliseconds. In-plane resolution 3 × 3 mm^2 (13201).

further down the fetal trunk. As before, the spinal canal can be seen posteriorly in the fetus with the vertebral body, the aorta, and the inferior vena cava anterior to it. To either side of these structures the central portions of the kidneys are clearly seen, particularly in the left kidney; also the renal pelvis and vessels coming from the kidney can easily be resolved. Fluid can be seen in the first part of the fetal small bowel, but the majority of the anterior abdomen is occupied by the fetal liver on the right and loops of bowel on the left. In Fig. 5, *3*, the slice has been taken further down the trunk. The lower poles of the kidneys can still be seen but the remainder of the abdomen is filled with loops of bowel. The fetal thighs have appeared within the amniotic fluid, with the dark central areas representing cross sections of the femur surrounded by the higher signal of the muscle bundles. Fat surrounds these structures, and because the fat signal is suppressed, they are outlined well against the high-signal amniotic fluid.

Fig. 6 is the final sequence taken from the same patient as seen in Fig. 5. These pictures are shown at 10 mm intervals through the fetal pelvis. In Fig. 6, *1*, the pelvis and right leg are outlined within the high-signal amniotic fluid. The structure of the femur can be seen clearly, including the head and neck of the bone, showing as a dark, low-signal area within the fetal thigh. Growing bone within the fetal knee shows as a high-signal area in both the femur and the upper tibia. Muscle groups can be seen within the fetal leg and in the gluteal regions. In Fig. 6, *2*, the joint space in the right knee is seen particularly clearly as a low-signal area between the femur and the tibia. The upper part of the bladder is beginning to appear as a high-signal area within the pelvis. A dark rim of low-signal fat is shown in the fetal buttock. In Fig. 6, *3*, the left leg is seen clearly. The fetal bladder is shown as a high-signal area within the pelvis, demonstrating the urine within it. The low-signal buttock fat is still present, but, in addition, the low signal of the sacral and iliac parts of the pelvis is seen posteriorly and to either side within the fetal pelvis.

Comment

Conventional magnetic resonance imaging of fetuses in the second and third trimesters of pregnancy has been performed for several years with a commercial machine that uses slower imaging techniques.[14, 15] However, because of fetal movement and the relatively long imaging times, blurring of the pictures occurs. Although fetal detail has been displayed occasionally, re-



Fig. 6. Three echo-planar imaging snapshots showing coronal views of fetal limbs and pelvis. **1** and **2,** Right femur, tibia, and pelvic girdle. **3,** Left leg, pelvis, and bladder. (Note maternal kidneys and spine.) Imaging time 64 milliseconds. In-plane resolution 3 × 3 mm^2 (13301).

liable measurements are not possible. As the fetus becomes larger, with increasing gestation, more detail becomes apparent. However, the internal structure of the fetus is seen very poorly and the standard nuclear magnetic resonance techniques provide relatively disappointing results apart from location of the placenta.[15]

Echo-planar imaging is a major advance over conventional magnetic resonance imaging. In this article some of the first motion-free magnetic resonance images of the human fetus in utero are shown. The images acquired with echo-planar techniques give a snapshot image in a fraction of a second, and consequently motion of the fetus is frozen in time. Different fast magnetic resonance imaging techniques are being developed by others,[17, 18] but these methods are currently unable to compete on speed.

The internal structure of many fetal organs is seen clearly, and as this experimental technique improves, there is considerable potential for the study of the internal structure of the organs in utero. Accurate measurements can be made of fetal organ volumes, for example, lung and liver volumes, which may be of considerable clinical importance when premature delivery is contemplated or the fetus is thought to be growth-retarded. Echo-planar imaging has already beeen used to measure lung volume in infants.[16] The multiparametric magnetic resonance image with specific pulse sequences allows a high level of tissue characterization, which makes this technique a useful adjunct to ultrasonography. In particular the differentiation between fats and other structures in the fetus will be useful, especially in studying development of the growth-retarded fetus.

Current echo-planar images have a slightly lower spatial resolution than ultrasonography, but tissue contrast and specificity are higher and the pictures are far easier to interpret than those obtained with ultrasonography. We believe that echo-planar magnetic resonance imaging has considerable potential for intrauterine assessment of the human fetus, in both normal and abnormal pregnancies.

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Hyperkalemia after irradiation of packed red blood cells: Possible effects with intravascular fetal transfusion

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Plasma potassium, calcium, and albumin concentrations in irradiated blood, and in fetal blood before and after transfusion, were measured. Dangerously high plasma potassium levels were observed in some units of irradiated packed red blood cells (range, 13.9 to 66.5 mEq/L; mean, 44.7 mEq/L) and could be one possible explanation for the high incidence of fetal arrhythmia associated with fetal intravascular transfusion. There are many factors operative in the preparation of irradiated packed red blood cells that may predispose to high potassium levels: the age of the red blood cells, the number of procedures used to concentrate the blood, the duration of time elapsed from concentration, the duration of time elapsed from irradiation, and the hematocrit. Use of fresh blood, avoidance of multiple packing procedures, limiting the hematocrit in the donor unit to ≤80%, and minimizing the time between concentration, irradiation and transfusion may minimize the potassium levels, and therefore making an additional washing procedure unnecessary. (Am J Obstet Gynecol 1990;163:607-9.)

Key words: Hyperkalemia, fetal intravascular transfusion, irradiation of packed red blood cells

Irradiation of blood before transfusion of the fetus and neonate is important because it effectively prevents graft versus host disease. Recent reports suggest that irradiation results in hyperkalemia in the donor plasma.[1-4] Ramirez et al.[1] found plasma potassium levels to be 53 mEq/L after irradiation and 4 days of storage, compared with a control value of 17 mEq/L. Two other studies[2,3] reported similar elevations of potassium after irradiation and found that potassium levels could be significantly reduced by manual washing procedures. These elevated potassium levels may cause dangerously high plasma concentrations in the fetus or neonate.[3,4] A 24-week fetus weighing 600 gm has a circulating fetoplacental blood volume of approximately 96 ml. Blood transfusions in excess of 50 ml/kg fetal weight are being performed by us and others. If such a fetus (hematocrit = 20% and plasma potassium = 3.5 mEq/L) receives 30 ml of transfused blood (hematocrit = 80% and plasma potassium = 50 mEq/L), the potassium bolus into the central vein exceeds the total plasma potassium of the entire fetoplacental unit. This massive potassium bolus injected into a central vein of an already compromised fetus may account for the high frequency of fetal arrhythmia associated with intravascular fetal transfusions.[3] Fetal arrhythmias associated with intravascular transfusion may be lethal.[3] Other factors including the temperature of transfused blood, volume transfused, citrate concentrations, and calcium levels may also predispose to fetal arrhythmia during intravascular transfusion.

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6/1/21549

Table I. Potassium, calcium, and albumin in donor blood and in fetal blood before and after transfusion

	Mean ± SD	*N*
Potassium in donated blood (mEq/L)	44.7 ± 17.9	8
Pretransfusion fetal potassium (mEq/L)	3.3 ± 0.3	4
Posttransfusion fetal potassium (mEq/L)	4.1 ± 0.7*	6
Calcium in donated blood (mEq/L)	8.2 ± 0.8	5
Pretransfusion fetal calcium (mEq/L)	8.9 ± 0.1	3
Posttransfusion fetal calcium (mEq/L)	9.1 ± 0.3	3
Albumin in donated blood (gm/dl)	3.0 ± 0.2	5
Pretransfusion fetal albumin (gm/dl)	2.3 ± 0.2	3
Posttransfusion fetal albumin (gm/dl)	2.0 ± 0.8	3

*Significantly increased from pretransfusion value, $p < 0.05$ by t test.

Table II. Factors predicting plasma potassium levels in units of irradiated packed red blood cells ($n = 8$)

	Mean ± SD	*t Value*	*p Value**
Age of unit before radiation (hr)	93.0 ± 27.0	0.50	0.64
Time between radiation and transfusion (hr)	12.6 ± 6.7	2.50	0.06
Hematocrit of unit (%)	77.0 ± 8.8	3.00	0.04

*The p value is determined by multivariate regression analysis with plasma potassium in the irradiated packed red blood cells used as the dependent variable and each of the three factors used as the independent variables.

Table III. Effect of a single concentrating procedure versus two concentrating procedures on plasma potassium of fresh blood

No. of procedures	*n*	*Hematocrit (%)*	*Potassium (mEq/L)*
1	9	74.7	4.0
2	4	91.3*	5.5*

*These values are significantly increased when compared with the values obtained after only one concentrating procedure ($p < 0.001$ by t test).

Methods

Recently we measured potassium, calcium, and albumin concentrations in irradiated blood and in fetal blood before and after transfusion (Table I). Potassium levels in units of irradiated packed red blood cells ranged from 13.9 to 66.5 mEq/L (mean, 44.7 mEq/L; SD = 17.9 mEq/L; $n = 8$). Large boluses of intravenous potassium in the fetus do not appear to cause a sustained increase in serum potassium, presumably because of tissue equilibration, renal excretion, and placental transfer. We have observed a fetal potassium increase from 3.2 mEq/L before transfusion to 5.3 mEq/L after transfusion, without resultant fetal arrhythmia. In another fetus we transfused 54 ml of blood with a serum potassium of 66.5 mEq/L to a 1550 gm fetus without evidence of arrhythmia. The equivalent volume of hyperkalemic solution injected rapidly into the central vein of an adult would be very dangerous. We have seen four transient fetal arrhythmias during or after 42 intravascular transfusions. Since we began monitoring fetal potassium levels, only one of seven transfusions was associated with a fetal arrhythmia. This one instance of transient bradycardia occurred immediately after transfusion of 75 ml of donor blood with a plasma potassium of 58 mEq/L to an 800 gm fetus.

Results

Multivariate regression analysis was performed to determine which of the following factors (age of the unit of blood before irradiation, hematocrit of the unit of packed red blood cells, and the time between irradiation of blood and transfusion) correlated best with the plasma potassium of the donor blood. Both the hematocrit of the unit of packed red blood cells and the duration of time between irradiation and transfusion correlated best (Table II). The three highest plasma potassium levels (66.5, 65.3, and 58.0 mEq/L) were associated with the three highest hematocrits (86%, 84%, and 84%, respectively). The lowest plasma potassium in the donor blood (13.9 mEq/L) was observed when the duration of time from irradiation to transfusion was only 3 hours. However, in one unit of blood we observed only a minimal rise in potassium, from 36 mEq/L 2 hours after irradiation to only 44.3 mEq/L 24 hours after irradiation. Therefore there appears to be other factors involved with the rise in potassium levels.

Because the variance in the plasma potassium of the donated blood could not be explained entirely by the hematocrit of the donor blood or the time elapsed after irradiation, we sought other explanations. We found that the regional blood center had concentrated some units of blood a second time to achieve a higher he-

matocrit. To further clarify this issue we studied nine additional units of fresh blood (≤5 days of age), five of which were centrifuged only once, and four of which were centrifuged twice and had plasma removed after each centrifugation (Table III). The hematocrit and potassium levels were significantly elevated ($p < 0.001$) after the second centrifugation. This probably occurred because the highly concentrated units had additional plasma removed. There was less plasma available for distribution of the potassium leaking out of the irradiated red blood cells. In addition, the removal of more anticoagulant-preservative solution resulted in less adenosine and glucose to support sodium-potassium adenosine triphosphatase. Inhibition of this enzyme would further accentuate potassium leakage.

Comment

There appear to be many factors operative in the preparation of irradiated packed red blood cells that may predispose to high potassium levels: the age of the red blood cells, the number of procedures used to concentrate the blood, the duration of time elapsed from concentration, the duration of time elapsed from irradiation, and the hematocrit. We conclude that each of these factors may contribute to cause a slow potassium leak in the red blood cell membrane, therefore causing a rising plasma potassium. Manual washing of irradiated packed red blood cells with saline solution significantly reduces the donor plasma potassium. This procedure is technically cumbersome and adds further time delay and expense. Use of fresh blood, avoidance of multiple packing procedures, and minimizing the time between concentration, irradiation, and transfusion may keep the potassium levels low, therefore making an additional washing procedure unnecessary. Further study is necessary to determine how much potassium can be safely administered during intravascular transfusion, and to determine if washing techniques are necessary.

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Lymphocyte proliferative response to fertilization antigen in patients with antisperm antibodies

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The fertilization antigen, immunopurified from human testes, activated lymphocytes from three of the six men and women with antisperm antibodies. Lymphocytes from none of the six men and women without antibodies were activated with fertilization antigen. Another sperm surface antigen, the germ cell antigen, immunopurified from murine testes, did not activate lymphocytes from any of the individuals with or without antisperm antibodies. These results indicate that the men and women with antisperm antibodies are sensitized against fertilization antigen and not germ cell antigen. These results reinforce our previous findings on the involvement of fertilization antigen in immunoinfertility in humans. (AM J OBSTET GYNECOL 1990;163:610-3.)

Key words: Antisperm antibodies, sperm antigens, cell-mediated immune responses, immunocontraception

Cell-mediated immune responses are readily induced to foreign cellular and viral antigens.[1, 2] Studies regarding the occurrence of cell-mediated immune responses to sperm, however, have claimed conflicting results. There are reports indicating the inability,[3] or conversely, ability[4, 5] of sperm (allogeneic or autologous) to activate lymphocytes. These conflicting data may possibly be a result of the presence of defective or dead sperm combined with motile sperm in the activating preparation, failure to remove somatic cells from semen before analysis, and the use of nonhuman sera.[6] One approach to evaluate whether sperm induce lymphocyte proliferation is to use sperm-specific antigens.

We have isolated and characterized a sperm-specific glycoprotein, the fertilization antigen from human and murine male germ cell plasma membranes.[7] The tissue-specific but species-cross-reactive monoclonal antibody to fertilization antigen inhibits human sperm penetration of zona-free hamster ova and blocks fertilization of murine oocytes by murine sperm.[8] The fertilization antigen is also involved in involuntary immunoinfertility in humans.[9, 10]

We have isolated and characterized another sperm antigen, the germ-cell antigen, from male germ cell plasma membranes.[11] The antibodies to germ cell antigen cause postfertilization reduction of fertility in rabbits and mice by inhibiting early embryonic development.[12] The antibodies to germ cell antigen bind to human sperm but do not inhibit penetration of zona-free hamster eggs. It has not been tested whether the immunoinfertile patients have antibodies to germ cell antigen.

The purpose of this study was to investigate whether these two well-defined sperm antigens (fertilization antigen purified from human testes and germ cell antigen purified from murine testes) could activate lymphocytes from immunoinfertile patients. In general, these studies were directed at exploration of the cell-mediated immune responses to sperm antigens and investigation of the involvement of fertilization antigen in immunoinfertility in humans.

Material and methods

Antigens

Fertilization antigen. Fertilization antigen was purified from lithium diiodosalicylate–solubilized human testes by immunoaffinity chromatography involving monoclonal antibodies that inhibit fertilization.[7, 8] Two-dimensional polyacrylamide gel electrophoresis, high-performance liquid chromatography, density gradient ultracentrifugation, and amino acid analysis indicated that purified antigenic molecule is composed of a monomer of 23,000 d and/or a dimer of 47,000 to 50,000 d.[9] Each batch of fertilization antigen was tested for its homogeneity. Only those batches that showed specific bands of 23,000 d and/or 47,000 to 50,000 d in sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) were used in this study. Fertilization antigen primarily showed its dimeric form.

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Germ cell antigen. Germ cell antigen was purified from lithium diiodosalicylate–solubilized murine testes with immunoaffinity chromatography involving monoclonal antibodies that cause postfertilization inhibition of fertility.[11, 12] After washing the unbound proteins with phosphate buffer (0.1 mol/L) at pH 8, the bound proteins were stepwise eluted with glycine–hydrochloric acid buffer (0.1 mol/L) first at pH 4 and then at pH 2.8. The peak eluted at pH 2.8 was neutralized with 1 mol/L potassium phosphate, concentrated, dialyzed against lithium chloride and then against phosphate-buffered saline solution (0.1 mol/L, pH 7.4), and frozen (−70° C) until further use. Only those batches that showed specific band of 63,000 d in nonreduced SDS-PAGE were used.

Polyacrylamide gel electrophoresis. The slab SDS-PAGE containing 10% gel was run under nonreducing conditions according to the method of Laemmli.[13] The gels were stained with Coomassie blue R, silver nitrate, or both stains.

Subjects. Peripheral blood mononuclear cells and sera were collected from six infertile adults (four men and two women) who had positive cultures for antisperm antibodies. Cultures from all subjects were negative for bacteria in the semen or cervix. Six fertile adults (one man and five women) without antisperm antibodies in the sera were also included as controls.

Sperm antibody assay. The presence of antibodies in sera was determined by the indirect Immunobead binding assay with isotype-specific reagents.[14] A positive test was defined as binding to at least 40% of the motile sperm.

Lymphocyte proliferative assay. Peripheral blood mononuclear cells were isolated from heparinized blood by Ficoll-hypaque gradient centrifugation.[6] Washed cells were incubated in wells of a microtiter plate containing, in a final volume of 0.2 ml, 2×10^5 peripheral blood mononuclear cells, 10% fetal bovine serum in RPMI 1640 medium with 25 mmol/L Hepes buffer, and L-glutamine supplemented with penicillin (100 U/ml), streptomycin (100 μg/ml), and kanamycin (100 μg/ml) and containing 1.2 to 2.4 μg of the antigen protein (fertilization antigen or germ cell antigen). After 6 days of incubation at 37° C, the cultures were pulsed with ^{3}H-thymidine (0.2 μCi per well) and harvested 18 hours later. Each sample was analyzed in triplicate for isotope incorporation into peripheral blood mononuclear cells. Blank samples consisting of cultures without the test antigens and positive controls consisting of cultures incubated with concanavalin A instead of sperm antigens were always analyzed in parallel with the test samples. Results were converted to a stimulation index according to the following formula: Stimulation index = Counts per minute in presence of antigen/Counts per minute in absence of antigen. A stimulation index >2 was considered evidence of specific stimulation.

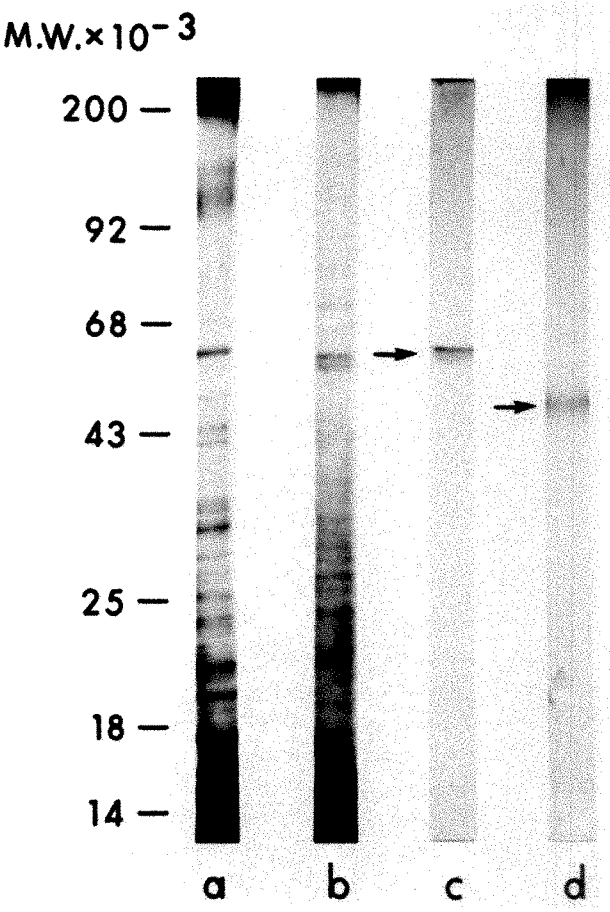


Fig. 1. The nonreduced SDS-PAGE pattern of the antigenic preparations stained with silver nitrate. Fertilization antigen showed a single band (↑) of 47,000 to 50,000 d (dimer) *(lane d)*. Germ cell antigen showed a single band (↑) of 63,000 d *(lane c)*. The lithium diiodosalicylate–solubilized human testes preparation *(lane a)* and lithium diiodosalicylate–solubilized murine testes preparation *(lane b)*, from which fertilization antigen and germ cell antigen, respectively, were purified, showed numerous bands of various molecular identities. The gels were calibrated with prestained molecular weight markers.

Statistical analysis. Differences between the stimulation indices of the control and antibody-positive lymphocytes were evaluated with unpaired Student's *t* test.

Results

The immunoaffinity-purified fertilization antigen showed a single band of 47,000 to 50,000 d (dimeric form) (Fig. 1, lane d), whereas germ cell antigen demonstrated a single band of 63,000 d (Fig. 1, lane c) in nonreduced SDS-PAGE. The lithium diiodosalicylate–solubilized human testes (Fig. 1, lane a) and lithium diiodosalicylate–solubilized murine testes (Fig. 1, lane b) demonstrated numerous bands of various molecular identities.

Table I. Lymphocyte proliferative response to sperm antigens

	Sex	Sperm antibodies	Stimulation index	
			Human fertilization antigen	*Mouse germ cell antigen*
Control No.				
1	F	—	0.9	0.2
2	F	—	0.6	0.4
3	F	—	1.0	1.0
4	F	—	0.4	0.2
5	F	—	0.6	0.4
6	M	—	0.7	—
Patient No.				
1	F	IgG	2.1	0.4
2	F	IgG	1.3	0.2
3	M	IgG, IgA	1.4	0.8
4	M	IgG	4.3	0.9
5	M	IgG	3.6	0.8
6	M	IgG	1.4	0.9

Peripheral blood mononuclear cells (2×10^5 per well) were incubated in RPMI 1640 medium containing 10% fetal bovine serum with or without 1.2 to 2.4 μg of the test antigen. Cultures were pulsed with ^{3}H-thymidine after 6 days and harvested 18 hours later. Positive reactions (stimulation index >2) have been underscored.

When investigated for their ability to activate lymphocytes, the purified antigens (fertilization antigen and germ cell antigen) yielded different results (Table I). Lymphocytes from none of the six fertile controls (men and women), who had no antisperm antibodies in sera, were activated with either antigen. In contrast, lymphocytes from three of the six patients with antisperm antibodies (men and women) were activated (>2, stimulation index) with fertilization antigen to various degrees. The remaining three showed some stimulation; however, the stimulation index was <2. Overall, the antibody-positive group showed a significantly ($p < 0.001$) higher stimulation index (mean ± SD, 2.35 ± 1.29) as compared with the antibody-negative group (mean ± SD, 0.70 ± 0.22). The germ cell antigen did not stimulate lymphocytes from either infertile patients with antibodies or fertile controls without antibodies (Table I). Overall, the stimulation index of the antibody-positive group (mean ± SD, 0.67 ± 0.29) was statistically insignificant compared with the antibody-negative group (mean ± SD, 0.44 ± 0.33). Lymphocytes from all the infertile patients with antibodies and fertile controls without antibodies responded equally well (stimulation index >2) to concanavalin A; the difference between the two populations was statistically insignificant.

Comment

Our data indicate that lymphocytes from some of the infertile patients with antisperm antibodies are sensitized to fertilization antigen. Lymphocytes from three of the six patients were activated with fertilization antigen as demonstrated by a stimulation index >2. Lymphocytes from both men and women with antisperm antibodies showed activation indicating the autosensitization and isosensitization of lymphocytes with this sperm antigen. Lymphocytes from none of the six fertile controls were activated with fertilization antigen, indicating that they were not sensitized against fertilization antigen. These data agree with our previous findings that fertilization antigen showed a strong reactivity with sera from immunoinfertile patients and did not react with sera from fertile controls.[9, 10]

In contrast to fertilization antigen, a second sperm antigen, germ cell antigen, did not activate lymphocytes from infertile men and women with antisperm antibodies, indicating that they were not sensitized to germ cell antigen. Similar results were obtained with lymphocytes from controls without sperm antibodies. Although germ cell antigen used in this study was isolated from murine testes, antibodies to germ cell antigen cross react with human sperm antigen. These results indicate that infertile subjects with antisperm antibodies may not be sensitized to all the sperm antigens.

The lymphocytes used in this study were a mixture of T cells and B cells. In another study in mice, we have shown that T lymphocytes presensitized to fertilization antigen in vivo secrete soluble factors on activation with this antigen in vitro.[15] These soluble mediators activated macrophages, and significantly inhibited sperm motility and embryonic development. Further analysis of the soluble factors indicated high levels of interferon-γ and tumor necrosis factor in addition to other undefined factors. These studies suggest that sperm antigens such as fertilization antigen may induce cell-mediated immune factors that may have detrimental effects on sperm motility and preimplantation embryonic development. Possible mechanisms of early-stage miscarriage related to a woman's sensitization to sperm have recently been proposed.[16, 17]

In conclusion, our data indicate that lymphocytes from infertile men and women with antisperm antibodies are sensitized to fertilization antigen and not to germ cell antigen. This further implicates the involvement of fertilization antigen in immunoinfertility in humans. This is the first report indicating the sensitization of lymphocytes from infertile patients against a purified sperm antigen.

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Effects on bone of surgical menopause and estrogen therapy with or without progesterone replacement in cynomolgus monkeys

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The influence of estrogen replacement therapy on bone loss of surgically postmenopausal cynomolgus macaques was evaluated histomorphometrically using the first (L-1) lumbar vertebra and ex vivo dual photon absorptiometry of the third (L-3) lumbar vertebra. The animals were a subgroup of a larger study on the effects of estrogen replacement therapy on diet-induced coronary artery atherosclerosis. The three experimental conditions were as follows: untreated females with oophorectomy, females with oophorectomy treated with continuous estrogen replacement therapy plus cyclic progesterone, and females with oophorectomy treated with estrogen replacement therapy. Bone mineral density (grams per square centimeter) of L-3, when covaried for body mass index (body mass index, body weight/(trunk length/100)^2), was significantly lower for the oophorectomy group compared with the group treated by estrogen replacement therapy plus progesterone and estrogen replacement therapy groups ($p = 0.018$). When covaried for body mass index, trabecular bone volume percentage of a midsagittal section of L-1 was not significantly different between groups, but the adjusted mean was greatest in the estrogen replacement therapy plus progesterone group, followed closely by the estrogen replacement therapy group, and was least in the oophorectomy group. When covaried for body mass index, trabecular plate number was significantly lower ($p = 0.022$) and mean trabecular plate separation was significantly higher ($p = 0.033$) in the oophorectomy group. Thus both estrogen replacement therapy and estrogen replacement therapy plus progesterone provided overall protection against surgical menopause–associated bone mass loss. Cynomolgus macaques are an extremely useful animal model for estrogen replacement therapy use in prevention of postmenopausal bone loss. (Am J Obstet Gynecol 1990;193:614-8.)

Key words: Monkeys, oophorectomy, 17β-estradiol, progesterone, bone histomorphometry, dual photon absorptiometry

Osteoporosis is a common disease in which bone tissue, bone mass, or both is reduced, increasing the risk of fractures.[1, 2] Osteoporosis affects as many as 15 to 20 million individuals in the United States and leads to an estimated 1.3 million bone fractures a year.[2] The annual direct costs of osteoporosis incurred by American women aged 45 years and older in 1986 are estimated at $5.2 billion dollars.[1] Women are at greater risk of developing osteoporosis than men, and women's risk increases if they are naturally or surgically postmenopausal, probably as a result of the well-known accelerated, but transient, bone loss phase resulting from estrogen deficiency. The osteoporosis risk for women increases further if they are small, slender or nonathletic, if they are white or Asiatic, if they smoke, or drink excessive amounts of coffee or alcohol.[1, 2] Some of the osteoporosis risk factors are also associated with increased risk of coronary heart disease or death.[3] Consequently, appropriate treatment for osteoporosis should focus both on prevention or slowing the loss of bone mass and decreasing the risk of coronary heart disease. We concur with Hillner et al.[4] that any treatment regimen for postmenopausal osteoporosis that omits its cardiovascular consequences markedly underestimates the potential gains from therapy.

In 1984 the National Institutes of Health Consensus Conference on Osteoporosis recommended estrogen replacement therapy, increased consumption of calcium, and weight-bearing exercise for postmenopausal

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women.[2] Conversely, estrogen replacement therapy supplemented with progesterone currently is a widely recommended form of therapy.[2, 5] There is convincing evidence that progesterone supplementation is associated with a reduction in endometrial cancer risk in women receiving estrogen replacement therapy.[2, 5] Progesterone supplementation also may augment the beneficial effects of estrogens in providing protection against osteoporosis.[5] Other forms of therapy that often are directed at a particular event in the bone remodeling cycle include oral calcitriol, intranasal calcitonin, and fluoride therapy.[2] However, only therapies that include estrogen in their regimen seem to provide multisystemic benefits. Estrogen replacement therapy is effective in prevention and treatment of osteoporosis,[2] and in reducing the risk of coronary heart disease.[5]

Transdermal or subdermal 17β-estradiol (via implants) has been recommended as a way to provide adequate estrogen replacement therapy[6, 7] because it results in serum estrogen patterns typical of the early follicular phase of the menstrual cycle (estradiol/estrone ratio of approximately 1.0[8]) and because it prevents the hepatic first-pass presentation of estrogen that may be associated with perturbation of lipoprotein metabolism and coagulation.[8] We report the results of an experiment designed to study the benefits of estrogen replacement therapy with or without cyclic progesterone in the prevention of trabecular bone loss. Effects on coronary artery atherosclerosis are reported elsewhere.[6] This study should provide the basis for further studies of therapeutic regimens that would concurrently benefit the skeletal and cardiovascular systems.

Material and methods

Animals. The animals were subjects in a large experiment designed to study the inhibition of diet-induced coronary artery atherosclerosis by estrogen replacement therapy or estrogen replacement therapy plus progesterone in surgically postmenopausal cynomolgus monkeys *(Macaca fascicularis)*.[6] Thirty-nine randomly chosen animals were used for the bone studies. These feral animals were imported from Jakarta, Indonesia (Hazelton Research Products, Denver, Pa.). Cynomolgus macaques have been established as a model of postmenopausal or postoophorectomy bone loss[9-11] and are extremely useful in studies of reproductive hormone influences on coronary artery atherosclerosis.[6, 12, 13]

Experimental design and procedures. The animals were kept in social groups consisting of four or five females in indoor-outdoor pens measuring 2.0 × 3.2 × 2.5 m. The animals had water ad libitum and for 30 months were fed a moderately atherogenic semipurified diet that contained 2.5 IU of vitamin D_3 per gram of diet with a 1.17 calcium to phosphorus ratio (591 mg of calcium and 503 mg of phosphorus per 100 gm of food). The vitamin D_3 content and calcium and phosphorus ratio of the diet were appropriate for this group of young adult female macaques. The animals had bilateral oophorectomy 4 months after initiation of the diet regimen. Guidelines established by our institutional Animal Care and Use Committee, state and federal laws, and standards of the Department of Health and Human Services were followed throughout the experiment. The animals were randomly assigned to one of three experimental groups: *group 1*—untreated females, that had oophorectomy (n = 12); *group 2*—females that had oophorectomy that were treated with estrogen (1,3,5(10)-estratrien-3,17β-diol, Steraloids, Inc., Wilton, N.H.) plus cyclic progesterone (4-pregnene-3,20-dione, Steraloids, Inc.) replacement therapy (n = 15); and *group 3*—females that had oophorectomy and were treated with estrogen replacement (n = 12). The hormones were administered beginning 1 month after oophorectomy via subcutaneously implanted silicone rubber tubing. The estrogen implants had an inner diameter of 0.335 cm and an outer diameter of 0.465 cm, were 3.0 cm in length, and were filled with 17β-estradiol. The estrogen implant remained in the animals for the entire 25-month treatment period. During alternating 28-day periods, the animals in the estrogen plus progesterone group received a second implant (3.5 cm long) filled with progesterone.[6] Although this combination did not mimic the normal menstrual cycle, it provided for midfollicular phase estradiol concentrations and progesterone levels similar to those observed in the peak of the luteal phase. The oophorectomy group received subcutaneous implants of empty silicone rubber tubing (3 cm long) that were left in place for the duration of the treatment period. Every quarter, estrogen and progesterone plasma concentrations were determined to evaluate the adequacy of the hormone delivery system. Serum estrogen and progesterone were measured by radioimmunoassays described previously.[13]

Tissue collection and histomorphometry. At the end of the experimental period the animals were killed and necropsied. The lumbar spine was removed and cleaned of soft tissue. The dorsal arches, spinous processes, and spinal cord were removed. The lumbar vertebral bodies were transected longitudinally and fixed in 70% ethanol. Half of the L-1 vertebral body was stained in Osteochrome Villanueva stain (Polysciences, Warrington, Pa.), processed, and embedded in methyl methacrylate as described previously.[14] Blocks were sectioned midsagittally at 5 to 7 μm with a Jung-K microtome, mounted, deplasticized in xylene, and counterstained with toluidine blue before coverslipping and coding. The trabecular bone area was marked at least 1 mm away from the cortical borders, and read by one

Table I. Densitometric dual photon absorptiometry data from L-3 vertebral bodies obtained from female cynomolgus macaques that had oophorectomy and hormone replacement

Group	*Mean*	*SEM*	*Mean**	*n*
L-3 bone mineral content (gm)				
Oophorectomy	0.705	0.04	0.683	10
Estrogen replacement therapy plus progesterone	0.873	0.07	0.844	9
Estrogen replacement therapy	0.720	0.05	0.773	9
L-3 bone mineral density (gm/cm^2)				
Oophorectomy	0.269	0.01	0.262†	10
Estrogen replacement therapy plus progesterone	0.333	0.02	0.323	9
Estrogen replacement therapy	0.280	0.02	0.299	9

*Mean adjusted by animal's body mass index.

†$p < 0.05$ between adjusted group means of the oophorectomy and estrogen plus progesterone groups.

of us (M. J.). Measurements were made as described previously,[14] with a microscope equipped with a camera lucida and a computer using the Bioquant IV (R & M Biometrics, Nashville) digitizing software. Primary measurements were taken directly and included total tissue area or volume (trabecular bone plus marrow tissue) with a mean total volume of 24.44 mm^2 (SEM = 1.24); bone area or bone volume with a mean of 5.75 mm^2 (SEM = 0.35); and bone surface or perimeter with a mean of 97.32 mm (SEM = 5.01). Structural static parameters derived from primary data included L-1 trabecular bone volume percent, L-1 trabecular thickness (micrometers), L-1 trabecular number (per millimeter), and L-1 trabecular separation (micrometers).[14-16]

Ex vivo densitometry. The rest of the lumbar vertebrae were kept in 70% ethanol. Most of the longitudinally intact L-3 vertebral bodies were scanned ex vivo with a dual photon absorptiometer (Norland model 2600, Fort Atkins, Wis.). All the L-3 dual photon absorptiometry scans were performed and analyzed by one of us (S. R.). The longitudinally cut L-3 vertebral bodies were aligned and secured with rubber bands. The segments were placed ventrodorsally (the normal positioning of a live scan) on a plastic water-filled bag (approximately 2.5 cm thick) on a 6.0-mm-thick piece of Plexiglas and on top of the scanner pad. The water and Plexiglas combination modeled the absent baseline soft tissue (Rs value = 1.45*). This combination has been reported previously and provides the best ex vivo accuracy and precision.[17] Bone mineral content (in grams) and bone mineral density (grams per square centimeter) were recorded. The lumbar scans were taken at a 1.0 mm point resolution with 1.0 mm line spacing, a scan speed of 5.0 mm/sec, and a scan width of 4.0 cm. One L-3 vertebra had dual photon absorptiometry scanning 10 times for precision. The coefficient of variation for L-3 bone mineral content was 2.69% and 2.39% for L-3 bone mineral density.

*Rs is the ratio of the attenuation coefficients of the two energy beams and ranges from 1.30 (pure adipose tissue) to 1.48 (pure muscle tissue).[17]

Statistics. At necropsy the body weight of monkeys receiving estrogen replacement therapy was significantly less ($F_{2,36} = 5.37$, $p < 0.01$) than that of the animals in the other two groups by analysis of variance (BMDP Statistical Software, University of California, Berkeley, Calif.). The difference in body weight was due to the initial experimental group randomization and was not an experimental result. Correction of the various measurements for body weight without regard to the animal's height (trunk length, suprasternal notch to the pubic symphysis length in centimeters) may not be a valid method of comparing the groups. Consequently, body mass index [body weight/(trunk length/100)^2] was used as a covariate in the analyses. Means and SEM were calculated and reported for each variable. Logarithmic transformation created normality for all data. Analysis of covariance was used in the comparison of L-3 bone mineral content, L-3 bone mineral density, L-1 trabecular bone volume, L-1 trabecular bone thickness, L-1 trabecular number, and L-1 trabecular separation. Post hoc comparison between adjusted group means was performed by Tukey's test for each significantly different ($p < 0.05$ by analysis of covariance) variable.

Results

Plasma hormones. Animals that received estrogen replacement therapy (both estrogen replacement therapy and estrogen replacement therapy plus progesterone had a mean estrogen level of 221 pg/ml (SEM = 22) and those in the oophorectomy group had less than the assay's lower limit (<20 pg/ml). Mean progesterone levels during the periods of replacement ther-

Table II. Histomorphometric data from midsagittal sections of L-1 vertebral bodies of female cynomolgus macaques that had oophorectomy and hormone replacement

Group	*Mean*	*SEM*	*Mean**	*n*
L-1 trabecular bone volume (%)				
Oophorectomy	22.01	1.02	21.87	12
Estrogen replacement therapy plus progesterone	24.97	1.17	24.72	15
Estrogen replacement therapy	22.63	1.31	23.08	12
L-1 trabecular bone thickness (μm)				
Oophorectomy	92.18	3.15	92.73	12
Estrogen replacement therapy plus progesterone	96.93	4.49	97.96	15
Estrogen replacement therapy	86.22	4.99	84.40	12
L-1 trabecular bone number (No./mm)				
Oophorectomy	2.39	0.06	2.36†	12
Estrogen replacement therapy plus progesterone	2.59	0.08	2.54	15
Estrogen replacement therapy	2.65	0.10	2.73	12
L-1 trabecular bone separation (μm)				
Oophorectomy	329.95	12.24	333.51	12
Estrogen replacement therapy plus progesterone	293.61	10.77	300.26	15
Estrogen replacement therapy	297.92	13.48	286.03	12

*Mean adjusted by animal's body mass index.

†$p < 0.05$ between adjusted group means of the oophorectomy and estrogen replacement therapy groups.

apy were 9.3 ng/ml (SEM = 0.6) in the estrogen replacement therapy plus progesterone group and 0.8 ng/ml (SEM = 0.1) in the other two groups.[7]

Ex vivo dual photon absorptiometry. Dual photon absorptiometry data are summarized in Table I. For L-3 bone mineral content, no overall significant difference was found ($F_{2,24} = 2.45$; $p = 0.107$). An overall significant difference was found for L-3 bone mineral density ($F_{2,24} = 4.78$; $p = 0.018$), with significant differences between adjusted group means of the oophorectomy and estrogen replacement therapy plus progesterone groups ($p < 0.05$). No significant densitometric differences were observed between the estrogen replacement therapy and estrogen replacement therapy plus progesterone groups.

Histomorphometry. Histomorphometric results are summarized in Table II. There was no significant difference between groups of L-1 trabecular bone volume ($F_{2,35} = 1.47$; $p = 0.244$), but the estrogen replacement therapy plus progesterone group had the greatest trabecular bone volume, the estrogen replacement therapy group had less, and the oophorectomy group had the least volume even after the means were adjusted for body mass index. The L-1 trabecular bone thickness was not significantly different ($F_{2,35} = 1.87$; $p = 0.169$). However, an overall significant difference ($F_{2,35} = 4.29$; $p = 0.022$) was found for L-1 trabecular number, with significant differences between the adjusted means of the oophorectomy and estrogen replacement therapy groups ($p < 0.05$). The L-1 trabecular separation also was significantly different overall ($F_{2,35} = 3.76$; $p = 0.033$). No significant histomorphometric differences were observed between the estrogen replacement therapy and estrogen replacement therapy plus progesterone groups.

Comment

The mechanism of the action of sex hormones on bone cells is unknown and presently is an area of intense research. Both estrogens and progestins have been reported as responsible in the maintenance of bone mass in postmenopausal osteoporosis[18] and even postmenopausal use of estrogen alone has been protective against subsequent fracture in women.[19]

Histomorphometric and densitometric studies yielded similar patterns of group differences with the estrogen replacement therapy and estrogen replacement therapy plus progesterone groups having the greatest bone mineral density and trabecular bone volume of all the groups, even after body mass index adjustment. As expected, the oophorectomy group had the lowest bone values for all the histomorphometric and bone densitometric measures. Both estrogen replacement therapy and estrogen replacement therapy plus progesterone protected against oophorectomy-induced bone loss measured by either method.

Adams et al.[6] reported a significantly greater overall

extent of diet-induced coronary artery atherosclerosis in female macaques that had oophorectomy without hormone replacement. Small doses of transdermal estradiol may be as effective as oral estrogens in preventing bone loss[7] and in decreasing the risk for coronary disease.[20] Although in human and nonhuman primate females atherosclerotic plaque formation and osteopenia both are related to loss of ovarian function, each event might be the result of variable and separate mechanisms. Natural menopause has an unfavorable effect on lipid metabolism, which may contribute to an increase in the risk of coronary disease.[20] A relationship between abnormal lipid metabolism and osteoporosis presently is not known, but hormonal receptors and increased cytokine activity in bone cells are believed to be involved primarily in postmenopausal bone loss.

Hormone therapy, given for 2 years and beginning immediately after oophorectomy, appears to protect against oophorectomy-induced bone loss and coronary artery atherosclerosis in cynomolgus macaques.

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Embryopathic effects of short-term exposure to hypoglycemia in mouse embryos in vitro

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The effect of short-term hypoglycemia was studied at two stages of development in postimplantation mouse embryos in vitro. Day 8 (gastrulating) mouse embryos were placed in hypoglycemic medium (60, 80, 100, or 110 mg/dl glucose) for 4 hours in which normoglycemia (120 to 150 mg/dl glucose) was restored for the remaining 44 hours of culture. Day 9 (neurulating) mouse embryos were exposed to hypoglycemia (20, 40, 60, or 80 mg/dl glucose) for 2, 4, 6, or 24 hours followed by normoglycemia for the remainder of 24 hours. At the end of culture embryos were evaluated for growth and malformations and compared with controls grown in normoglycemic medium. The results show that a 50% reduction in glucose for as little as 2 hours causes dysmorphogenesis in neurulating mouse embryos, whereas longer exposure times, more severe levels of hypoglycemia, or both are required to affect growth. Furthermore, gastrulating embryos are more sensitive to short periods of hypoglycemia than those undergoing neurulation. (Am J Obstet Gynecol 1990;163:619-24.)

Key words: Short-term hypoglycemia, malformations, mouse embryos, gastrulation, neurulation

The current approach to clinical management of the pregnant patient with insulin-dependent diabetes favors strict glycemic control instituted before conception and maintained throughout pregnancy in an attempt to reduce the incidence of malformations and perinatal mortality associated with this disease.[1, 2] As a result of aggressive management, patients with insulin-dependent diabetes are more likely to experience severe and prolonged episodes of hypoglycemia.[3, 4]

Compared with other metabolic alterations of diabetes, the teratogenicity of hypoglycemia has not been well studied. Clinical studies of pregnant human patients with insulin-dependent diabetes have yielded equivocal results concerning the potential role of hypoglycemia in congenital malformations.[4, 5] In vivo studies in rodents[6-8] have generally involved prolonged maternal hypoglycemia in which duration and level of embryonic exposure could not be accurately quantified or controlled. More recently in vitro studies have demonstrated malformations and growth retardation in rodent embryos cultured in hypoglycemic medium, but exposure times were for extended periods, generally 12 hours or longer.[8-11] In terms of embryonic development, these long exposures in rodent embryos represent several days of human gestation and therefore an unlikely duration of sustained hypoglycemia. The demonstration of malformations in rodent embryos exposed to hypoglycemia for 1 hour[12] or 8 hours in vitro[10] and 1 hour in vivo[13] suggests that short-term exposure to hypoglycemia does, in fact, interfere with normal development if the exposure occurs during critical periods of organogenesis. However, neither the minimum exposure time nor the level of hypoglycemia required to produce malformations has been defined.

Therefore this investigation evaluates the teratogenicity of short-term exposure to hypoglycemia in mouse embryos undergoing gastrulation and neurulation by systematic variations in glucose concentrations and durations of hypoglycemic exposure using whole embryo culture. This method allowed us to examine stage-dependent sensitivity to hypoglycemia and to specifically define exposure parameters at which dysmorphogenesis, growth retardation, or both occur in the mouse embryo model.

Material and methods

Whole embryo culture. The care and use of all animals in this study have been approved by the Institutional Care and Use Committee of the University of North Carolina, Chapel Hill. Randomly bred ICR mice were maintained on a 14-hour-light/10-hour-dark cycle and provided with food and water ad libitum. Females were checked for vaginal plugs the morning after overnight mating, and this day was designated day 1

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of pregnancy. Pregnant females were killed by cervical dislocation on the eighth or ninth day of gestation and the uterine horns were immediately removed and placed in Tyrode's buffer. Implantation sites were dissected with watchmakers' forceps to remove conceptuses from surrounding tissues. Embryos at the appropriate stage (day 8, primitive streak; day 9, three to five somites) surrounded by an intact visceral yolk sac and ectoplacental cone were placed in medium in 30 ml culture flasks on a rotating wheel at 30 rpm and 37° C.

Day 8 (primitive streak stage) mouse embryos were cultured four to a flask as described previously[14] in a combination of mouse serum, rat serum, and Tyrode's buffer for the first 24 hours of culture. Hypoglycemic medium was prepared with 25% serum from mice injected intraperitoneally with 5 IU regular insulin 1 hour before blood collection and 50% serum from rats injected intraperitoneally with 50 IU regular insulin 2 to 3 hours before blood collection. Serum was immediately centrifuged, heat inactivated, and treated with 2.5 μl/ml streptomycin and frozen at −20° C. The remaining 25% of culture medium consisted of Tyrode's buffer and sufficient concentrated (50 mg/ml) β-D-glucose to produce the appropriate glucose concentrations. Control medium was prepared in the same manner to produce glucose concentrations between 120 and 150 mg/dl, the normal range for rodents. Glucose measurements were made using a model 27 industrial analyzer (Yellow Springs Instruments, Yellow Springs, Ohio). After an initial 4-hour exposure to 60, 80, 100, 110, or 120 to 150 mg/dl glucose, the glucose concentration of the medium was measured and hypoglycemic medium was made normoglycemic (120 to 150 mg/dl glucose) for the remainder of the first 24 hours with the addition of a small amount of 50 mg/ml β-D-glucose. Embryos were then transferred individually to 2.5 ml normoglycemic medium containing 75% rat serum and 25% Tyrode's buffer for the second 24 hours in culture. Flasks were aerated at 12-hour intervals with a gas mixture of 5% oxygen, 5% carbon dioxide, and 90% nitrogen, and at 48 hours with 20% oxygen, 5% carbon dioxide, and 75% nitrogen. Cultures were terminated at 48 hours.

Day 9 embryos (three to five somites) were placed individually in 2.5 ml hypoglycemic or control medium. Hypoglycemic medium consisted of 75% serum from rats injected intraperitoneally with 50 IU regular insulin 2 to 3 hours before blood collection. The remaining 25% consisted of Tyrode's buffer and a small amount of 50 mg/ml β-D-glucose, as necessary, to produce the appropriate glucose concentrations. Control medium was prepared in the same manner, or with 75% normal rat serum and 25% Tyrode's buffer; both methods produced glucose concentrations between 120 and 150 mg/dl. Treated embryos were exposed to 20, 40, 60, or 80 mg/dl glucose for 2, 4, or 6 hours; the glucose concentration of the medium was then measured, and a small amount of 50 mg/ml β-D-glucose was added to the medium to bring the glucose concentration to control levels (120 to 150 mg/dl) for the remainder of the 24-hour culture period. Additional embryos were exposed to each level of hypoglycemia for the entire 24-hour culture period. Treated embryos were compared with controls cultured for 24 hours in normoglycemic medium. Flasks were aerated initially and at 12 hours with 5% oxygen, 5% carbon dioxide, and 90% nitrogen and at 24 hours with 20% oxygen, 5% carbon dioxide, and 75% nitrogen. Cultures were terminated at 24 hours.

Assessment of embryos. Embryos were removed from culture (day 8, 48 hours; day 9, 24 hours) and examined under a dissecting microscope for gross malformations, rotation, heartbeat and circulation, and somite number. The majority of embryos in each group were frozen for total protein determination according to the Lowry method[15] as an assessment of embryonic growth. Several embryos were processed for scanning electron microscopy to illustrate representative malformations using Sorenson's glutaraldehyde fixative and osmium postfixation followed by dehydration in graded alcohols, critical point drying, and argon coating. Statistical analysis was performed with an analysis of variance.

Results

Day 8 embryos. Control embryos placed in culture at day 8 (primitive streak stage) and grown for 48 hours attained a size and conformation similar to that of day 9 control embryos grown for 24 hours (i.e., the normal morphologic features of day 10 embryos; Fig. 1, *1* and *3*). Ten of 64 (14%) day 8 control embryos failed to grow normally and exhibited incomplete rotation, exencephaly, or both.

Day 8 embryos exposed to 4 hours of hypoglycemia followed by normoglycemia for the remainder of 48 hours showed high malformation rates at all glucose concentrations tested (60, 80, 100, and 110 mg/dl). Defects included poor overall growth and rotation, failure of cranial neural tube expansion and closure, dysmorphic optic primordia, and incomplete cardiac looping (Fig. 1, *2*). Total protein measurements and somite numbers showed a significant growth retardation of day 8 embryos after short-term exposure to hypoglycemia (Table I), and both dysmorphogenesis and growth retardation were more severe in day 8 than day 9 embryos after comparable hypoglycemic exposures.

Glucose concentrations decreased by a mean 2.2 mg/dl in hypoglycemic media and 4.0 mg/dl in control media during the first 4 hours of culture.

Day 9 embryos. No difference was observed in the

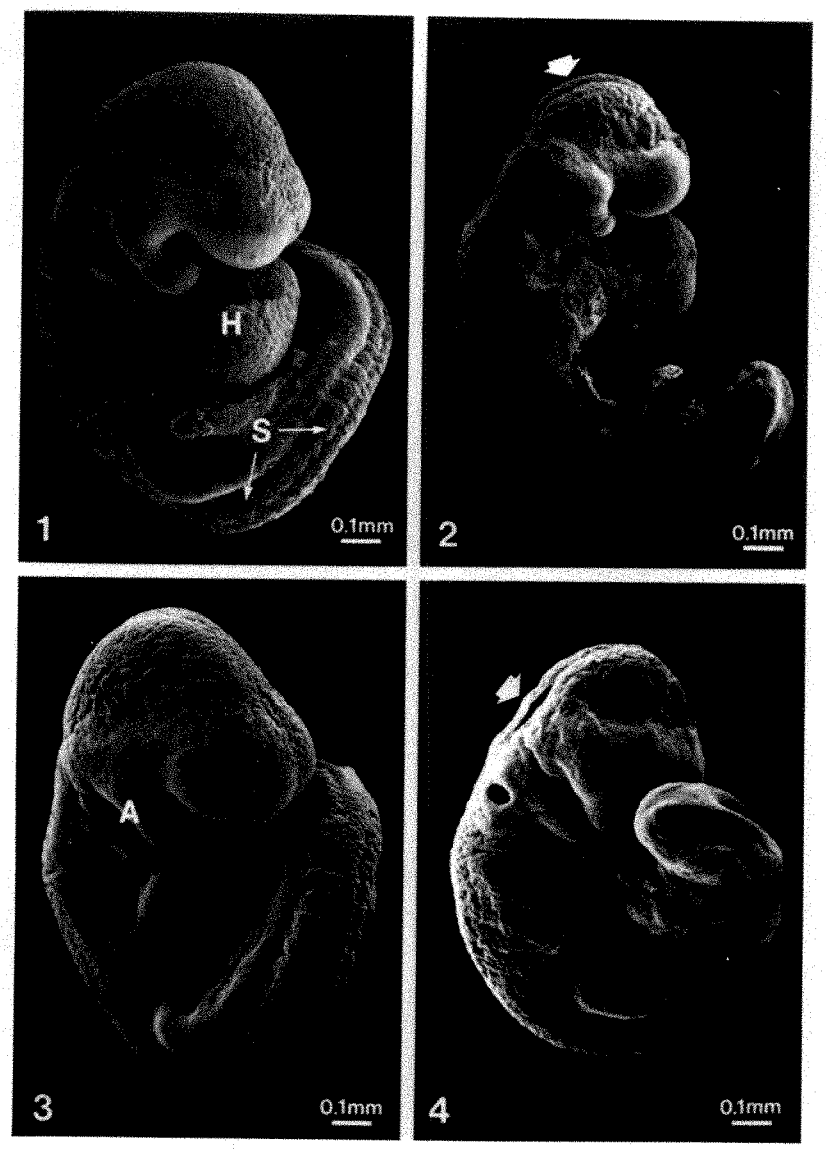


Fig. 1. 1, Day 8 (gastrulation stage) mouse embryo cultured 48 hours in normoglycemic medium showing normal rotation, closed and expanded cranial neural tube, and 20 to 23 somite pairs. Heart *(H)*, somites *(S)*. (×70). **2,** Day 8 mouse embryo cultured 4 hours in hypoglycemic medium (60 mg/dl glucose) and 44 hours in normoglycemic medium showing incomplete growth and rotation, failure of cranial neural tube expansion and closure *(arrow)*, and abnormal cardiac looping. (×70). **3,** Day 9 (three to five somite pairs) mouse embryo cultured 24 hours in normoglycemic medium showing normal rotation, closed and expanded cranial neural tube, and 20 to 23 somite pairs. (×70). **4,** Day 9 mouse embryo cultured 4 hours in hypoglycemic medium (60 mg/dl) and 20 hours in normoglycemic medium showing incomplete expansion and closure of cranial neural tube *(arrow)*, abnormal closure of posterior neuropore, and 20 to 22 somite pairs. (×70).

growth and development of day 9 (three to five somites) mouse embryos cultured for 24 hours in control medium (120 to 150 mg/dl glucose) from normal serum or glucose-supplemented serum collected from rats treated with insulin. Embryos rotated into a fetal-like position and developed a regular heartbeat and visceral yolk sac circulation. Somite pairs increased to 18 to 22, and the neural tube closed completely (Fig. 1, *3*) with the exception of the posterior neuropore, which normally remains open at this stage of development. One of 53 (1.9%) control embryos failed to develop normally and exhibited exencephaly and a narrow optic vesicle.

Embryos exposed to hypoglycemia demonstrated deficiencies in rotation, heartbeat and circulation, somite number, and neural tube closure, particularly at lower glucose concentrations and longer periods of exposure (Table II). Gross malformations resulting from hypoglycemic exposure typically involved deficient expan-

Table I. Results of experiments in day 8 embryos

Glucose concentration	*Exposure time*	
	4 hr	*48 hr*
60 mg/dl		
Malformed (%) (n = 38)	71*	
Protein (μg, mean ± SE) (n = 23)	72.77 ± 6.85*	
Somites (No., mean ± SE) (n = 38)	16.7 ± 0.7*	
80 mg/dl		
Malformed (%) (n = 27)	78*	
Protein (μg, mean ± SE) (n = 27)	92.00 ± 9.71*	
Somites (No., mean ± SE) (n = 27)	16.8 ± 0.8*	
100 mg/dl		
Malformed (%) (n = 24)	63*	
Protein (μg, mean ± SE) (n = 24)	92.31 ± 10.04*	
Somites (No., mean ± SE) (n = 24)	19.0 ± 0.8*	
110 mg/dl		
Malformed (%) (n = 23)	52*	
Protein (μg, mean ± SE) (n = 23)	90.82 ± 6.05*	
Somites (No., mean ± SE) (n = 23)	19.7 ± 0.6*	
Control, 120-150 mg/dl		
Malformed (%) (n = 69)		14
Protein (μg, mean ± SE) (n = 58)		126.36 + 5.71
Somites (No., mean ± SE) (n = 69)		21.5 + 0.2

*$p < 0.05$

sion and closure of the cranial region of the neural tube (Fig. 1, *4*). Less frequent defects included abnormal closure of the posterior neuropore, dysmorphic or small optic primordia, hypoplastic visceral arches, incomplete cardiac looping, and pericardial swelling.

Malformation rates increased with longer exposure times at each level of hypoglycemia and were significantly elevated above the control level in all but the groups exposed to 80 mg/dl for 2 and 4 hours. In addition, for each period of hypoglycemic exposure, malformation rates increased as glucose concentrations decreased (Table II). A two-way analysis of variance demonstrated a significant interaction between glucose concentration and duration of hypoglycemic exposure with respect to malformation rates.

Embryonic growth was assessed by measuring total protein content and monitoring somitogenesis in individual embryos. Protein content was significantly decreased in embryos exposed to 20 or 40 mg/dl glucose for 4, 6, or 24 hours, and to 60 mg/dl for 24 hours compared with controls (Table II). A consistent trend in decreasing protein content with increasing duration of hypoglycemic exposure occurred in embryos cultured in 20, 40, or 60 mg/dl glucose. There was no decrease in protein content at any duration of exposure in embryos cultured in 80 mg/dl glucose. These results closely paralleled the effect of hypoglycemia on somitogenesis (Table II).

Glucose concentrations decreased by a mean 3.1 mg/dl in hypoglycemic media and 4.0 mg/dl in control media during the first 2 to 6 hours of culture.

Comment

The incidence of congenital malformations in the offspring of patients with insulin-dependent diabetes remains elevated despite current emphasis on improved metabolic control.[16] Recent clinical practices with intensive insulin therapy have increased the susceptibility of patients with insulin-dependent diabetes to hypoglycemic episodes,[3, 4] making hypoglycemia an important factor to consider for its teratogenic potential. The majority of previous investigations in this area have used exposure times in rodent embryos equivalent, in terms of developmental stages, to several days of human gestation (one day of mouse development is equivalent to approximately 5 days in the human). This study represents the first systematic evaluation of hypoglycemia in the mouse embryo model at levels and durations of hypoglycemia more consistent with those presumably experienced by embryos of human patients with insulin-dependent diabetes.

To define levels and durations of hypoglycemia that produce abnormal growth and development, we exposed day 9 (neurulating) mouse embryos in vitro to 20, 40, 60, and 80 mg/dl glucose, representing 16%, 32%, 48%, and 64%, respectively, of normal blood glucose in a pregnant mouse (125 mg/dl). Hypoglycemic exposures were for 2, 4, 6, and 24 hours, approximately equivalent to 8 to 10 hours, 16 to 20 hours, 24 to 30 hours, and 5 days, respectively, in terms of human embryonic development during the same period of neurulation.[17] Our results demonstrate that neurulating mouse embryos exposed for as little as 2 hours to glu-

Table II. Results of experiments in day 9 embryos

Glucose concentration	*Exposure time*			
	2 hr	*4 hr*	*6 hr*	*24 hr*
20 mg/dl				
Malformed (%)	46* (*n* = 13)	69* (*n* = 16)	100* (*n* = 16)	100* (*n* = 12)
Protein (μg, mean ± SE)	93.32 ± 9.68* (*n* = 11)	71.66 ± 3.77* (*n* = 11)	53.88 ± 5.88* (*n* = 10)	33.95 ± 2.08* (*n* = 11)
Somites (No., mean ± SE)	14.7 ± 1.1* (*n* = 13)	16.1 ± 0.3 (*n* = 16)	11.8 ± 1.2* (*n* = 16)	5.3 ± 0.4* (*n* = 12)
40 mg/dl				
Malformed (%)	31* (*n* = 13)	67* (*n* = 15)	100* (*n* = 25)	100* (*n* = 16)
Protein (μg, mean ± SE)	92.01 ± 6.04 (*n* = 13)	81.42 ± 6.14* (*n* = 13)	62.78 ± 4.67* (*n* = 17)	44.63 ± 6.64* (*n* = 12)
Somites (No., mean ± SE)	15.8 ± 0.4 (*n* = 13)	14.6 ± 1.1* (*n* = 15)	14.7 ± 0.7* (*n* = 25)	8.4 ± 0.9* (*n* = 16)
60 mg/dl				
Malformed (%)	23* (*n* = 13)	40* (*n* = 27)	60* (*n* = 17)	100* (*n* = 13)
Protein (μg, mean ± SE)	110.93 ± 6.59 (*n* = 13)	94.61 ± 7.04 (*n* = 11)	82.95 ± 7.91 (*n* = 11)	53.96 ± 2.85* (*n* = 12)
Somites (No., mean ± SE)	17.2 ± 0.2 (*n* = 13)	16.3 ± 0.5 (*n* = 27)	17.1 ± 0.3 (*n* = 17)	14.2 ± 1.0* (*n* = 13)
80 mg/dl				
Malformed (%)	13 (*n* = 15)	20 (*n* = 15)	27* (*n* = 15)	43* (*n* = 14)
Protein (μg, mean ± SE)	105.95 ± 3.86 (*n* = 14)	112.34 ± 7.32 (*n* = 15)	95.48 ± 4.86 (*n* = 15)	109.06 ± 6.15 (*n* = 14)
Somites (No., mean ± SE)	16.5 (*n* = 15)	16.5 (*n* = 15)	16.5 (*n* = 15)	16.2 (*n* = 14)
Control, 120-150 mg/dl				
Malformed (%)				2 (*n* = 66)
Protein, μg, mean ± SE)				96.48 ± 2.87 (*n* = 48)
Somites (No., mean ± SE)				16.7 ± 0.1 (*n* = 66)

*$p < 0.05$.

cose concentrations of 60 mg/dl or less show increased malformation rates when evaluated after 24 hours in culture. Growth retardation, as judged by total protein content and somitogenesis, occurs after 4 or more hours at glucose concentrations ≤40 mg/dl. Risk of dysmorphogenesis or growth retardation increases with increasing severity of exposure parameters (i.e., longer duration of hypoglycemia and lower glucose concentration).

Our results also suggest that younger, gastrulating embryos are more sensitive to short-term hypoglycemic exposure than those undergoing neurulation. Thus a 52% reduction (to 60 mg/dl) from normal glucose levels caused significantly elevated malformation rates in day 9 embryos, whereas a reduction of only 12% (to 110 mg/dl) from normal glucose levels produced abnormal growth and development in a significant number of day 8 embryos. Overall, day 8 embryos were more sensitive than day 9 embryos undergoing whole embryo culture, as evidenced by malformation rates of controls (14% vs 2%). This is consistent with previous studies and suggests a greater vulnerability of younger embryos to experimental manipulation.

Mammalian embryos are highly dependent on glucose as their primary energy source during the periods of gastrulation, neurulation, and early organogenesis[18] and are therefore sensitive to deficient glucose levels during these periods of development. Interestingly, hypoglycemia appears to have greater teratogenic potential than the more classic metabolic alterations of diabetes mellitus such as hyperglycemia and hyperketonemia. For example, glucose and ketone bodies must be experimentally elevated many times above normal levels for extended periods of time (24 to 48 hours) to cause consistent embryonic abnormalities in rodent embryos,[19, 20] whereas a 52% reduction from normal glucose levels is detrimental after only 2 hours in the neurulating mouse embryo. Therefore mild maternal hyperglycemia during early pregnancy may be less detrimental to the developing embryo than the risk of

hypoglycemic exposure resulting from overaggressive insulin therapy. Since stages immediately after implantation appear to be the most sensitive to induction of the diabetic embryopathy, management of the diabetic before conception is essential.

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Ovarian granulosa cell tumorigenesis in SWR-derived F1 hybrid mice: Preneoplastic follicular abnormality and malignant disease progression

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A high incidence (27.5%; 174 of 633) of spontaneous, malignant ovarian granulosa cell tumors develop in (SWR × SWXJ-9)F1 hybrid females between 3 and 6 weeks. Granulosa cell tumors developed in predictable stages, starting as preneoplastic lesions appearing as hyperemic follicles on the ovarian surface. These follicles were characterized by hypertrophied theca, degenerating oocytes, and large fluid- or erythrocyte-filled antra lined by irregular masses of granulosa cells. Rapidly proliferating granulosa cells filled the antra and the theca/interstitial cells became more dysplastic as granulosa cell tumors developed. Thus the morphology of the preneoplastic lesion suggests that disturbed mechanisms for normal follicular development underlie granulosa cell tumor initiation. Estradiol treatment before but not after preneoplastic lesions appeared inhibited granulosa cell tumor formation. By 6 to 9 months 42% of these mice show metastases in major abdominal and thoracic organs. Thus this model can be experimentally analyzed both for mechanisms of granulosa cell tumor initiation and subsequent malignant progression. (Am J Obstet Gynecol 1990;163:625-34.)

Key words: Mouse ovarian granulosa cell tumorigenesis, preneoplastic follicles, malignant progression

A novel mouse model for inherited susceptibility to granulosa cell tumors of the ovary has recently been described.[1-3] The granulosa cell tumors arise spontaneously in pubertal SWR/JBm, certain of their F1 hybrids, and some SWR × SJL derived recombinant inbred (SWXJ) strains of mice carrying the susceptible allele of *Gct* on chromosome 4.[3] Granulosa cell tumor incidence varies among strains and is governed by a small number of genes, some involving steroid metabolism regulation.[2] The SWR granulosa cell tumor bears a striking resemblance to human juvenile granulosa cell tumors found in young girls from infancy through menarche.[4, 5] Common features of this neoplasm in SWR mice and humans include early onset in ovaries with intact oocytes and follicles, depressed serum gonadotropins and aberrant steroidogenesis, similar histopathologic features of primary tumors, and malignant potential. Granulosa cell tumorigenesis in this model contrasts sharply with that found in other experimental and spontaneous rodent models in which oocyte deletion appears to be a prerequisite for tumor development.[6] In these models granulosa cell tumor formation is usually very slow and is preceded by mesothelial adenoma formation.[6] Furthermore, spontaneous granulosa cell tumors in mice[6] and rats[7] are typically unilateral and slow growing. Spontaneous granulosa cell tumors also occur in several domestic animal species, including cat, dog, sow, sheep, cow, and horse.[8, 9] Granulosa cell tumors also usually occur in adult animals, although cases in younger cats,[10] horses,[11] and calves[9] have been reported. In these species granulosa cell tumors are rarely bilateral and malignant potential varies with most malignancies found in mares and cats.[9]

Previous efforts to study the etiology of granulosa cell tumors in SWR-derived mice have been hampered by the relatively low spontaneous incidence found in susceptible strains.[1] In recent studies of genetic control of granulosa cell tumor susceptibility, a stock was created that is characterized by several features permitting investigations of all phases of granulosa cell tumorigenesis. The (SWR × SWXJ-9)F1 hybrid described in this article has a tightly circumscribed developmental age for granulosa cell tumor initiation, a remarkably high spontaneous granulosa cell tumor incidence, and marked potential for malignant progression. We describe the histopathology of preneoplastic ovaries, a longitudinal study of granulosa cell tumor development in mice identified as having macroscopic lesions in their

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ovaries at puberty, and the morphology and incidence of primary and metastatic granulosa cell tumors.

Material and method

Mice. Mice used in these experiments were maintained according to the guidelines for care and use of laboratory animals established by the National Institutes of Health. Matings were made between progenitor SWR strain (low granulosa cell tumor incidence) and SWXJ-9 strain (higher granulosa cell tumor incidence) mice.[1] Data in this report were gathered on (SWR × SWXJ-9)F1 hybrid female mice aged 3 weeks to 9 months. Mice were raised in a research colony at The Jackson Laboratory, maintained under 12-hour light-dark cycles. Mice were given pasteurized Wayne Lab Blox diet (crude protein, 24%; fat, 4%; fiber, 4.5%; ash, 5.9%; and vitamin and mineral fortified; Wayne Research Animal diets, Chicago) and chlorinated (10 to 20 ppm sodium hypochlorite; pH 2.8 to 3.2) water ad libitum. Two to four mice were housed in polycarbonate cages (13 × 28 × 15 cm) with white pine shavings for bedding. Granulosa cell tumorbearing mice retained for longitudinal studies were identified by aseptic laparotomy with the animals under general anesthesia (tribromoethanol, 0.25 mg/gm of body weight). Ovaries were exteriorized through bilateral flank incisions for inspection. After careful return of tumors or normal ovaries to the abdominal cavity, the muscle and skin wounds were surgically closed. Extra heat was provided for mice recovering from anesthesia before returning them to the animal room. Mice were killed by cervical dislocation for necropsy.

Preneoplastic lesions. The first studies were conducted to determine whether grossly apparent changes in juvenile ovarian morphology were predictive of granulosa cell tumor development and to characterize preneoplastic histologic changes associated with macroscopically identifiable lesions at various ages.

Experiment 1. To establish the prognostic validity of gross observations of preneoplastic ovaries, laparotomies were performed on groups of 50 to 60 mice at 28 or 42 days of age. Visual abnormalities of the ovary such as hyperemic follicles or granulosa cell tumor foci were noted, and mice were retained until 10 weeks of age when they were reinspected for granulosa cell tumors.

Experiment 2. To determine the sequence of morphologic changes during granulosa cell tumor development, separate groups of mice were killed at 22, 28, 32, 36, or 42 days of age. Biologic parameters of body, uterine, and ovarian weights and vaginal opening and cytology were determined to assess developmental status of mice at these ages. Ovaries were removed and fixed in Bouin's solution for routine histologic processing for light microscopy. Additional samples were fixed in Fekete's acid-alcohol formalin or neutral buffered 10% formalin, or were frozen before sectioning and stained with oil red O for lipid. Tissues were embedded in paraffin, sectioned at 6 μm, and sections were stained with hemotoxylin and eosin, ammoniacal silver for reticulin, Gomori's stain for iron, or periodic acid–Schiff stain for carbohydrate.

Experiment 3. To determine the effect of inhibiting ovulatory processes on granulosa cell tumor initiation, mice were treated with estradiol or cholesterol at 21 to 22 (preovulatory) or 29 to 36 (periovulatory) days of age. Mice were assigned to treatment groups by split-litter method, anesthetized as described above, and 1 cm silicone rubber capsules filled with cholesterol or 0.8% estradiol in cholesterol prepared as previously described[2] were surgically inserted beneath the skin in the scapular region. Necropsy was done at 56 to 70 days of age; body and organ weights, vaginal cytology, and presence of granulosa cell tumors were recorded. Representative ovaries were fixed for histologic examination.

Metastatic incidence and granulosa cell tumor morphologic features. To evaluate metastatic incidence, 65 pairs of granulosa cell tumor-bearing and littermate control mice were identified by laparotomy at 10 weeks of age and maintained until 7 to 9 months of age. Mice were weighed weekly and inspected for visible signs of advancing disease, such as poor coat quality, edematous appearance or sudden weight loss, pale ears indicative of anemia, lethargy, or labored breathing. Mice that appeared moribund were killed and inspected for metastases. Remaining mice were killed at indicated ages. Macroscopically visible nodules were recorded and fixed for histologic confirmation of granulosa cell tumor tissue. A subset of 15 (SWR × SWXJ-9)F1 mice with granulosa cell tumors were necropsied at 6 to 7 months of age for complete pathologic analyses. Ovaries, brain, lung, pancreas, stomach, duodenum, ileum, jejunum, cecum, colon, salivary glands, uterus, cervix, vagina, spleen, heart, esophagus, trachea, adrenal gland, both kidneys, skeletal muscle, liver, gall bladder, spinal cord, vertebrae, three sections of decalcified skull, urinary bladder, thymus, thyroid, and multiple lymph nodes were removed and fixed in Fekete's acid-alcohol formalin. Tissues were processed for light microscopy as previously described.

Results

Preneoplastic lesions

Experiment 1. In the study of preneoplastic progression, 12 of 57 (21%) mice examined at 28 days had macroscopically abnormal ovaries that were characterized by hyperemic follicles on the surface, but in most cases the ovaries were not enlarged. The ovaries of these 28-day F1 hybrid mice contained large antral fol-

licles; however, first ovulation had not occurred. At 10 weeks, 11 of the 12 (92%) ovaries with hyperemic follicles had progressed to granulosa cell tumors. One ovary had only an erythrocyte-filled cyst that was composed of a few layers of granulosa cells lining a cystic follicle. In addition, four mice with macroscopically normal ovaries at 28 days of age had granulosa cell tumors by 10 weeks of age. Thus the overall granulosa cell tumor incidence for this group of mice was 26.3% (15/57).

Twelve of 50 mice examined at 42 days of age had granulosa cell tumors that were characterized by an enlarged ovary with viable-appearing neoplastic tissue enclosed by the ovarian bursa, and striking increases in the ovarian vasculature. All of these mice still had granulosa cell tumors at 10 weeks of age. No additional tumors were found in mice that had normal ovaries at 42 days of age. Thus in (SWR × SWXJ-9)F1 mice, granulosa cell tumors develop between the third and sixth week of life, coincident with the transitional period of puberty.

Experiment 2. At 22 days of age all ovaries appeared normal by visual inspection, were small and kidney-shaped, with no corpora lutea visible. Histologic examination revealed that they were comprised mainly of primary follicles or follicles with several layers of granulosa cells. Formation of antral follicles was in early stages.

Between 28 and 32 days ovaries with preneoplastic lesions exhibited remarkably rapid changes in morphology. Several disturbances in follicular development of normal ovaries (Fig. 1, *a*) were observed. First, incipient granulosa cell tumor foci were observed in antral follicles (Fig. 1, *b*) with oocytes still present (Fig. 1, *c*). These follicles were characterized by degenerating oocytes frequently surrounded by proliferating granulosa cells in structures resembling an enlarged cumulus oophorus. Necrotic granulosa cells were observed at the base of this cellular mass and sometimes these masses were detached (verified in serial sections) from granulosa cells lining the antrum. Alternatively, the oocyte was also observed embedded in a proliferating mass of mural granulosa cells. Thus, tumorigenesis did not appear to be confined to a single type of granulosa cell. In other follicles wherein oocyte remnants were no longer visible, proliferating granulosa cells filled most of the follicular space (Fig. 1, *d*). By 32 days oocytes were not commonly observed in preneoplastic follicles. A second characteristic was the presence of erythrocytes in the antra of follicles. Capillaries were observed traversing the theca and penetrating the granulosa layers, providing a source for the blood (Fig. 2, *a*). A third feature was the loss of basement membrane demarcation between the preneoplastic follicle wall and the theca (Fig. 2, *b* and *c*). The thecal/insterstitial cell compartment was proliferating as evidenced by mitotic figures, became increasingly hypertrophied, and oil red O-stained sections revealed abundant, large lipid droplets. Granulosa cell lipid was also demonstrable but appeared in the form of very small droplets. During this period the demarcation between granulosa and theca layers became less distinct; theca and granulosa cells showed a tendency to interdigitate (Fig. 2, *b*). Granulosa cells at these borders appeared hypertrophied or necrotic (Fig. 2, *b* and *c*). In silver stained–sections, reticulum fibers were clearly observed in the theca, circumscribing the granulosa compartment of normal follicles as part of the basal lamina. Reticulum fibers were also prominent in the theca-interstitium of preneoplastic follicles but were no longer continuously delineating the granulosa compartment. The remaining nontumorous follicles in preneoplastic ovaries were small and most contained degenerating oocytes.

Many of the ovaries that did not have obvious preneoplastic lesions were characterized by multiple atretic antral follicles with prominent theca, degenerating oocytes, and granulosa cells with pyknotic nuclei.

At 36 days morphologic features transitional between preneoplasia and neoplasia were observed. Some of the aberrant follicles were filled with neoplastic granulosa cells showing multiple mitotic figures. Peripheral granulosa cells were frequently vacuolated and elongated toward the center of the cysts. In some instances, small patches of loosely adherent granulosa cells were detached from the granulosa cell mass and were found within venous or lymphatic channels. Other ovaries remained composed primarily of large hemorrhagic follicles with irregular layers of granulosa cells lining the cysts. Thecal cells were dysplastic and were either hypertrophied or retained an elongated fusiform shape. Mitotic figures were frequently observed. Some thecal interstitial cells were arranged in clusters of luteinized theca. Areas of hypertrophied thecal/interstitial cells not clearly associated with a developing granulosa cell tumor focus were sometimes observed. Staining with oil red O revealed the presence of lipid in these hypertrophied thecal cells. The contralateral ovary at this stage sometimes showed preneoplastic follicles. Alternatively, some ovaries appeared normal and showed evidence of recent ovulation and corpora lutea formation.

At 42 days a variety of morphologic patterns were observed in developing granulosa cell tumors. This appeared to be a time of rapid growth for most tumors. The most striking morphologic features were the large masses of granulosa cell tumor cells separated by small compressed patches of thecal/interstitial cells (Fig. 3, *a*) and the high number of mitotic figures (three to seven) per single high-power field (Fig. 3, *b*). In some

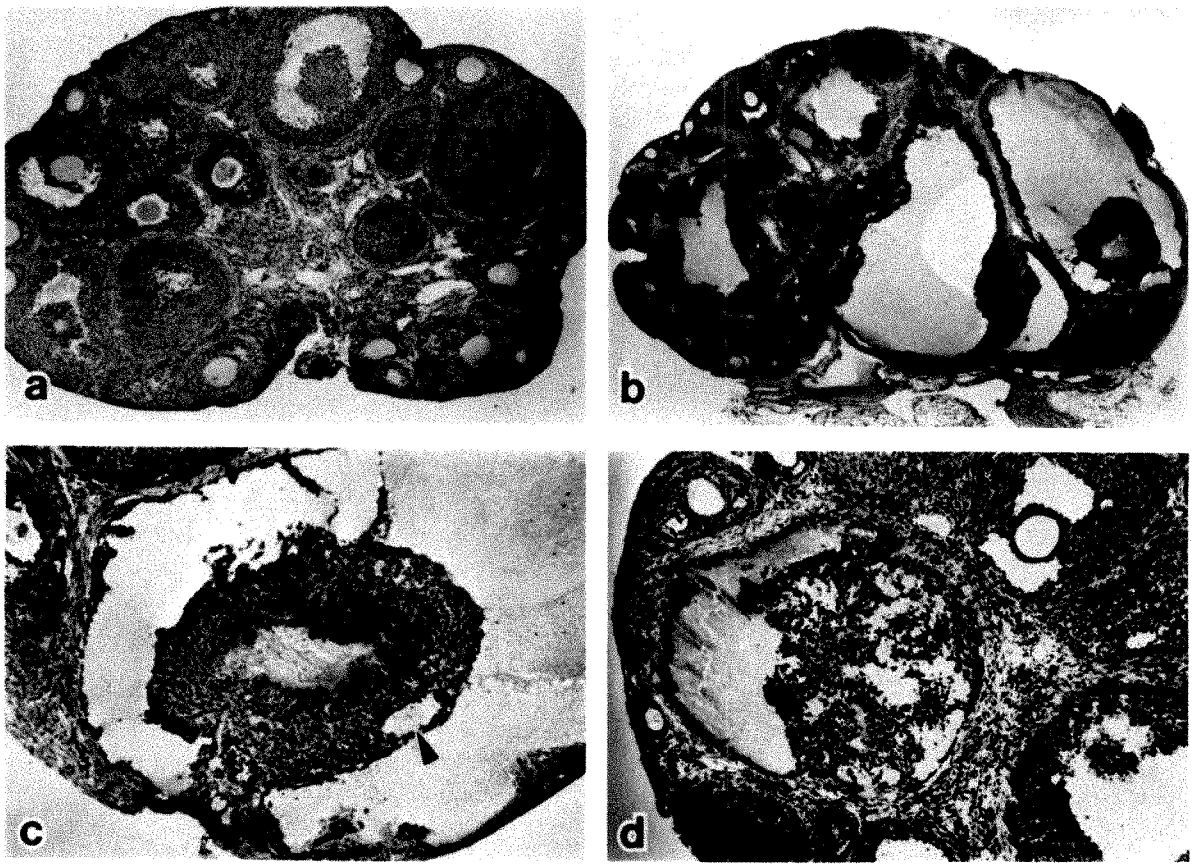


Fig. 1. Patterns of granulosa cell proliferation in preneoplastic follicles (28 to 32 days). **a,** Normal ovary from 28-day-old (SWR × SWXJ-9)F1 mouse. (Original magnification ×25.) **b,** Preneoplastic, 29-day ovary showing multifocal cystic follicles with granulosa cells arranged in multilayered irregular masses, rather than a single layer of flattened cells typical of polycystic ovarian disease. (Original magnification ×25.) **c,** Abnormal follicle with central mass of granulosa cells attached to follicle wall. The center of the mass contained erythrocytes and cellular debris, whereas a degenerating oocyte can be seen in the periphery of the mass *(arrow).* (Original magnification ×62.5.) **d,** Another 29-day ovary with a majority of this preneoplastic cystic follicle filled with loosely adherent granulosa cells. (Original magnification ×62.5.)

areas granulosa cell tumor cells were hypertrophied and resembled luteinized granulosa cells. Staining with oil red O revealed lipid accumulation in these cells. Some of the larger granulosa cell tumors had necrotic regions or individual cells with pyknotic nuclei. The pattern of granulosa cell tumor cell arrangement was either macrofollicular or solid, with areas of fluid- or erythrocyte-filled cysts. Areas of thecal/interstitial cell involvement were most clearly seen in slides stained for reticulum fibers. Reticulum fibers were observed surrounding thecal cells but were not seen in the rapidly proliferating granulosa cell masses. The degree of thecal involvement varied considerably but was not a prominent feature. The thecal/insterstitial cells were markedly hypertrophied, frequently vacuolated, and interdigitated with small blood vessels. In sections stained for iron, deposits were observed in cells within the thecal/interstitial compartment, but not within the granulosa cell tumor cell mass. In some cases small follicles with oocytes present were observed at the periphery of the granulosa cell tumor mass.

At 70 days of age granulosa cell tumors were characterized by a macrofollicular pattern encircled by thecal/interstitial tissue that varied in thickness from a few cell layers to thick areas of hypertrophied cells with foamy cytoplasm staining positively for lipid. In some regions of granulosa cell tumor cells, multiple mitotic figures were observed, whereas other areas of the tumors appeared quiescent in growth or undergoing necrosis. Variably sized erythrocyte- or glycoprotein-filled

cysts were prominent throughout the macrofollicular masses of tumor cells. In some cases normal primary follicles with degenerating oocytes, restricted to the periphery of the granulosa cell tumor mass, were observed.

In conjunction with the morphologic data gathered during the peripubertal period, measurements of reproductive maturation were also obtained from separate groups of mice. Table I shows that the interval from 22 to 38 days was a period of rapid ovarian steroidogenic development as evidenced by significant increases in ovarian and uterine weights and in the percentage of females with open vaginas. Thus preneoplastic lesions arose simultaneously with the onset of reproductive maturation.

Experiment 3. The results of estradiol treatment on granulosa cell tumor incidence are presented in Table II. There was a striking difference in the effect of estradiol on granulosa cell tumor incidence between the two age groups. At 21 to 22 days estradiol treatment significantly suppressed granulosa cell tumor incidence, whereas no effect was found in the 29- to 36-day old group. In this latter group, there was no apparent correlation between age at capsule insertion and granulosa cell tumor incidence. In contrast, estradiol exerted a similar effect on body weight and vaginal cytology in mice of both groups. Histologic examination of estradiol-treated nontumorous ovaries demonstrated that ovulation was blocked as evidenced by the absence of corpora lutea. Ovaries contained variably sized antral follicles, many of which showed signs of atresia, including granulosa cells with pyknotic nuclei, degenerating oocytes, and prominent theca. There was no evidence of preneoplastic follicles. Granulosa cell tumors from the estradiol-treated mice did not appear to differ morphologically from those found in the cholesterol-treated control mice. In contrast, ovaries from the cholesterol-treated mice were normal and they contained follicles in various stages of development and corpora lutea appropriate to cycling mice.

Metastatic progression

Frequency. The incidence of primary granulosa cell tumors in the (SWR × SWXJ-9)F1 mice at the time of writing is 27.5% (174/633). A group of 66 granulosa cell tumor host mice was used to establish metastatic incidence and primary granulosa cell tumor location. The data, presented in Table III, reveal that the majority of primary granulosa cell tumors were bilateral, with no trend for laterality in the remaining tumors. By 6 to 9 months of age primary and metastatic disease became lethal. There was a high percentage (42%) of mice with metastatic disease. Metastases were most com-

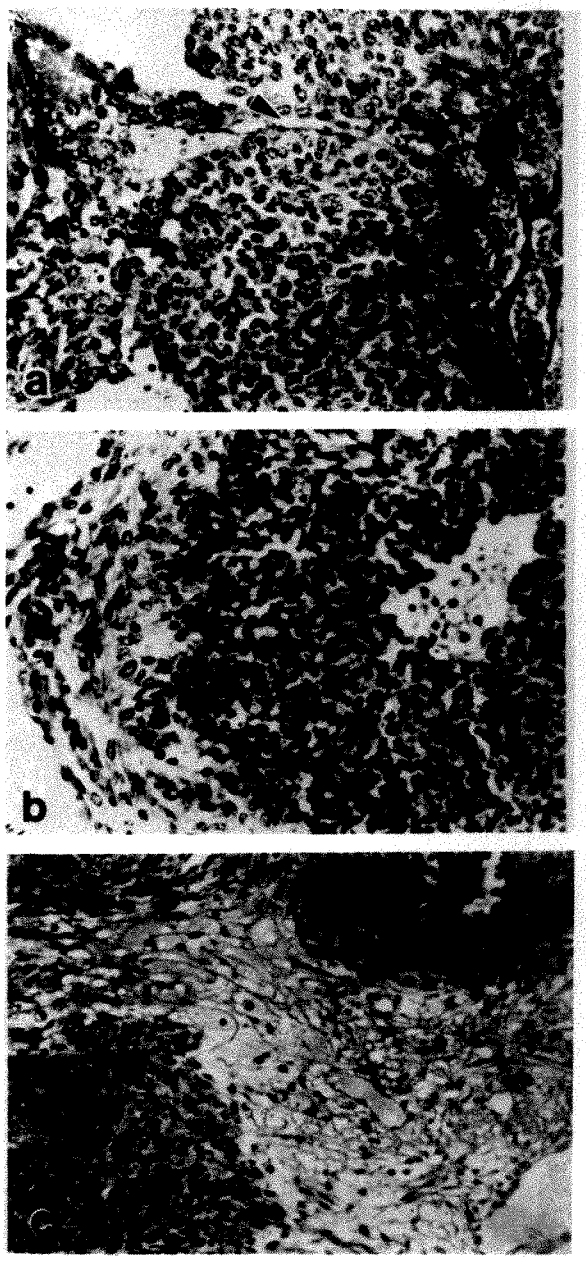


Fig. 2. Theca-interstitial cell patterns in preneoplastic ovaries (28 to 32 days). **a,** Blood vessel *(arrow)* penetrates wall of the preneoplastic follicle through the granulosa cells to the erythrocyte-filled center. (Original magnification × 156.) **b,** Necrosis of outer granulosa cell layers adjacent to hypertrophied theca. (Original magnification × 156.) There is no distinct separation of the theca and interstitial compartments, and the theca/interstitial cells are hypertrophied and dysplastic. **c,** Preneoplastic ovary from a 32-day-old mouse shows thecal/interstitial layer is profoundly hypertrophied, with much lipid accumulation. Normal follicular structures were severely disturbed in this ovary. Granulosa cells lining the theca-granulosa cell junction were elongated toward the center of the cyst and showed some cytoplasmic hypertrophy. (Original magnification × 125.)

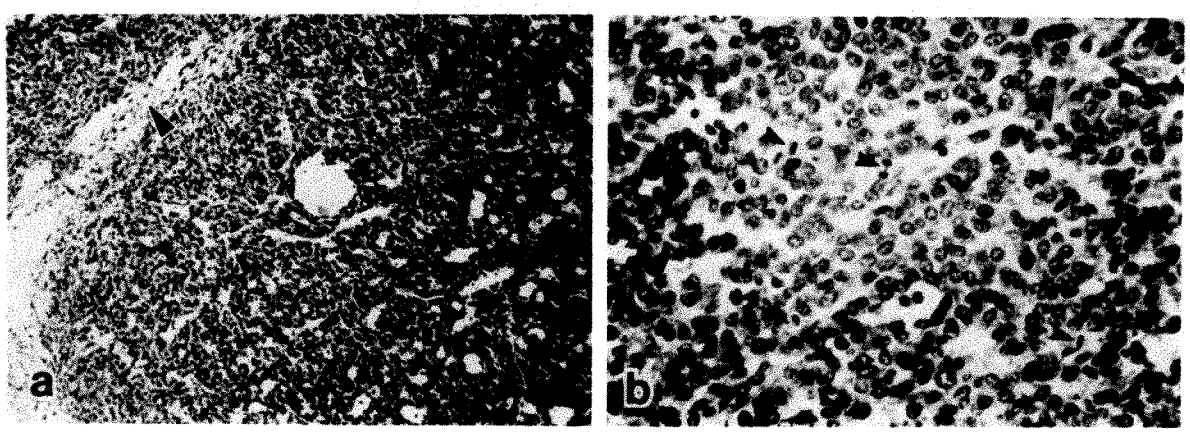


Fig. 3. Transitional neoplasia. **a,** Ovary from a 42-day-old mouse showing solid mass of granulosa cell tumor cells arranged in macrofollicular pattern with remnant of thecal/interstitial cells *(arrow)* separating "follicles." (Original magnification ×62.5.) Normal ovarian tissue was no longer visible in this ovary. **b,** Multiple mitotic figures observed in granulosa cell tumor mass of **a.** (Original magnification ×250.)

Table I. Reproductive maturation parameters for (SWR × SWXJ-9)F1 hybrid female mice without ovarian granulosa cell tumors

Age (days)	*Body weight (gm)*	*Ovarian weight (mg)*	*Uterine weight (mg)*	*Vagina open (%)*
22	8.70 ± 0.25	2.02 ± 0.11	8.18 ± 0.54	0
29	13.11 ± 0.40	3.18 ± 0.12	30.15 ± 5.22	92
38	15.91 ± 0.33	5.45 ± 0.21	80.21 ± 9.14	100

monly found within renal lymph nodes, liver, and lungs. Other tissues with a lower frequency of metastatic nodules include spleen, diaphragm, stomach, mediastinum, skeletal muscle, abdominal connective tissue, and muscle, kidney, and pancreatic lymph nodes. Tissue examined and found free of metastatic nodules were brain, small and large intestine, salivary glands, uterus, vagina, heart, esophagus, trachea, adrenal glands, urinary bladder, thymus, and thyroid gland. Ascites was occasionally observed in older granulosa cell tumor host mice.

Morphology. At necropsy primary granulosa cell tumors ranged in size from 3 to 4 mm to more than 25 mm in diameter. Twenty-six primary granulosa cell tumors had macroscopically evident moderate to extensive areas of necrosis. In rare instances a tumor appeared completely regressed. Regressed granulosa cell tumors showed focal necrosis, congestion of medium and large veins, and effacement by foamy round pigment-laden cells. Follicles containing oocytes were not present. Growing primary tumors consisted of retiform, micro- or macrofollicular patterns. Particularly in granulosa cell tumors with the microfollicular arrangement (Fig. 4, *a*), small spheroids of detached granulosa cells could be seen entering lymphatic or blood vessels (Fig. 4, *b*). Cells within these spheroids had frequent mitotic figures. Granulosa cells were characterized by scant amphophilic cytoplasm, small oval nuclei with coarsely clumped chromatin, and a single small nucleolus. Nuclear grooving was not observed in tissues fixed in Bouin's or Fekete's solutions. Structures resembling Call-Exner bodies, microcysts containing material that stained positive for glycoprotein by the periodic acid–Schiff stain, were also observed. Areas of necrosis, some with fibrin thrombi, were prominent in the larger tumors. The granulosa cell tumors also had large congested veins. An additional feature of all tumors was the presence of large, multinucleated, foamy cells—possibly macrophages—containing a diffuse golden brown pigment that stained positively for iron. Some of these cells also contained dark brown, finely granular cytoplasmic pigment. Small, scattered foci of osteoid were present in approximately half of the granulosa cell tumors (Fig. 4, *a*). These were always located in areas in which there were numerous lymphatics and small veins. Occasionally areas of luteinized thecoma, distinguished by positive staining for reticulum and lipid, were observed. Local invasion through the ovarian bursa was evident in all cases, indicating early visceral implantation of tumor cells.

The histologic appearance of metastatic nodules was strikingly similar to that of the primary granulosa cell tumors. Metastases often had a solid pattern with little evidence of necrosis and frequent mitotic figures. Less

Table II. Effects of estradiol treatment on granulosa cell tumor incidence, ovarian weights, and vaginal cytologic features in (SWR × SWXJ-9)F1 hybrid female mice

Age (days)	*Treatment*	*Tumor incidence**	*Body weight (gm)*	*Ovarian weight (mg)*	*Vaginal cytologic features*
21-22	Cholesterol	24/107	18.3 ± 0.2	8.2 ± 0.5	Cycling†
	Estradiol	3/104‡	16.5 ± 0.2§	4.7 ± 0.5§	Cornified
29-36	Cholesterol	16/43	20.9 ± 0.3	ND	Cycling
	Estradiol	14/42	18.5 ± 0.3§	ND	Cornified

ND, Not determined.
*Number of granulosa cell tumor hosts per total number of females examined.
†Cytologic patterns observed represented all stages of the estrous cycle.
‡Significantly different from control ($p < 0.01$, χ^2).
§Significantly different from control ($p < 0.001$, unpaired t test).

Table III. Progression of ovarian granulosa cell tumors to malignancy

*No. of primary granulosa cell tumor hosts**	*Tumor location*			*No. of metastatic granulosa cell tumor hosts*
	Right	*Left*	*Bilateral*	
66†	15/62 (24%)	13/62 (21%)	34/62 (55%)	28/66 (42%)

*Sixty-one littermate control females remained free of granulosa cell tumors at necropsy.
†Records on four granulosa cell tumor hosts lacked notes about location of tumors.

frequently, microfollicular (Fig. 4, *c*) or macrofollicular arrangements of granulosa cell tumor cells were observed. Very large metastatic nodules occasionally had areas of focal necrosis or accumulation of dark brown pigment.

Nontumorous contralateral ovaries were small in size and contained a small number of follicles with scattered individual cell necrosis and numerous small colloid-filled microcystic structures.

Comment

The (SWR × SWXJ-9)F1 hybrid has provided a unique opportunity to identify morphologic changes at all stages of granulosa cell tumorigenesis associated with tumor initiation, primary tumor development, and metastatic progression. In these F1 hybrid mice, granulosa cell tumors occur simultaneously with recruitment of the first group of follicles during ovarian maturation, form in antral follicles with intact oocytes, are commonly bilateral, grow rapidly, and become metastatic with high frequency.

The finding of macroscopically visible ovarian abnormalities that are prognostic for granulosa cell tumor development by 28 days of age permitted identification of tumor-destined individuals at preneoplastic stages. Histologic examination of such ovaries revealed features that were not observed in previous microscopic examination of established primary granulosa cell tumors in adult mice.[1] The development of morphologic abnormalities in preneoplastic ovaries offers some insights into mechanisms underlying granulosa cell tumorigenesis in the SWR model. First, within the follicular compartment, no ovarian abnormalities were detected at 22 days before formation of large antral follicles. Identifying preneoplastic changes just 6 to 7 days later defines this time as the beginning of the critical period for tumor initiation. Preneoplastic changes were initiated only in antral follicles, with degenerating oocytes often present. Normal follicles in earlier stages of development could be seen on the periphery of ovaries with developing granulosa cell tumors, and there was no evidence of neoplastic transformation of granulosa cells within these small follicles. Thus the granulosa cell tumor did not appear to grow by recruiting relatively undifferentiated granulosa cells from nearby normal follicles. This suggests that one or more of an array of intricately balanced endocrine, paracrine, and autocrine factors[12] regulating normal granulosa cell proliferation and differentiation may be part of granulosa cell tumor-initiating stimuli. Furthermore, only the relatively differentiated granulosa cells from antral follicles may be susceptible to tumor-initiating stimuli. This hypothesis is strengthened by the finding that granulosa cell tumor incidence was suppressed in these F1 hybrid mice by treatment with estradiol at 21 to 22 days before development of large antral follicles. Estradiol treatment also suppressed granulosa cell tumor initiation in SWXJ-9 progenitor strain mice.[1] Once the preneoplastic lesions had formed, estradiol did not prevent subsequent tumorigenesis. Thus we speculate that estrogen exerts an effect on the granulosa cell tumor-initiating stimuli rather

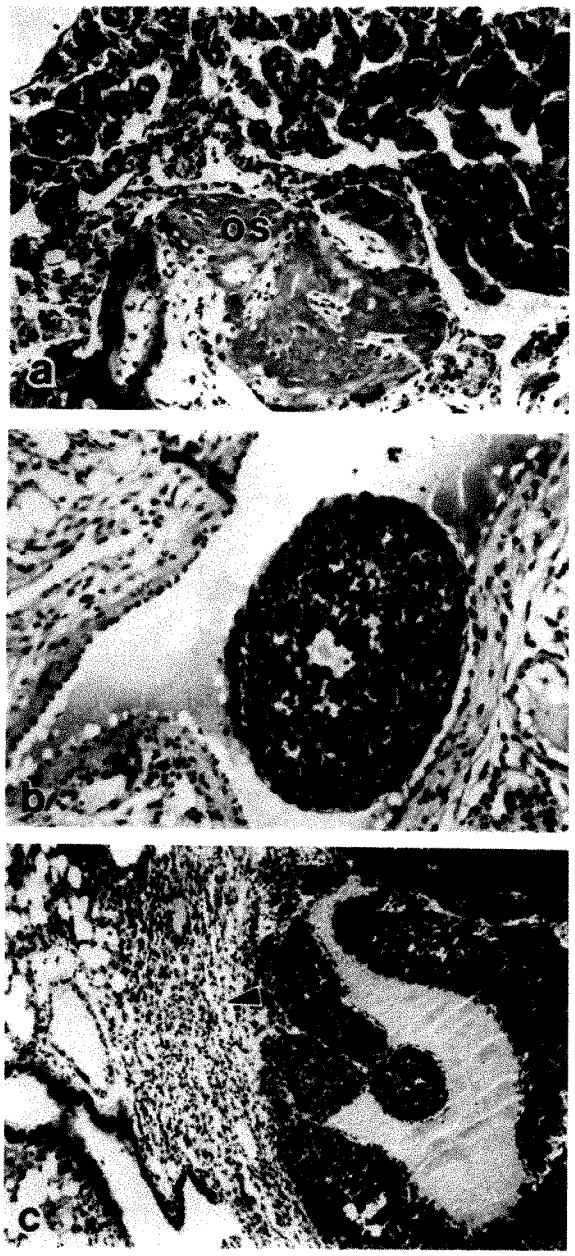


Fig. 4. Primary and metastatic granulosa cell tumors in adult mice. **a,** Primary granulosa cell tumor displaying microfollicular arrangement with adjacent osteoid (os) in central portion of tumor. Cells arranged in this pattern were bathed in serous or erythrocyte-filled fluid and had substantially less necrosis than cells arranged in more solid or macrofollicular patterns. (Original magnification ×156). **b,** Primary granulosa cell tumor nodule in lymphatic channel. (Original magnification ×125.) **c,** Pulmonary metastatic nodule compressing normal lung tissue *(arrow)* at left side of photomicrograph. The metastatic cells are arranged in pseudofollicular pattern with a peduncle of granulosa cell tumor cells reminiscent of those seen in preneoplastic follicles. (Original magnification ×62.5.)

than on tumor growth–supportive mechanisms. There are several ways in which estradiol could suppress granulosa cell tumor initiation. For example, estradiol treatment affects granulosa cell development both indirectly via suppression of pituitary gonadotropin release and directly via modulation of steroidogenic enzyme activities[13] and receptor numbers for gonadotropin and other growth factors.[12]

A second feature of preneoplastic lesions that offers insight into tumorigenic mechanisms is the hypertrophy and hyperplasia of the thecal/interstitial cell compartment. The recognition of abnormalties in this compartment during granulosa cell tumor initiation is an important finding because there are several likely interactions between thecal/interstitial cells and preneoplastic granulosa cells. For example, during the transition from immature to adult ovarian status, there are definitive changes in steroidogenesis as biologically less active products are replaced by more potent androgens and estrogens.[14] In normal adult ovaries, the thecal/interstitial cell compartment is the source of androgens, and hypertrophy of this compartment is associated with increased androgen production both in atretic follicles and in polycystic ovarian disease.[15] Androgens are also involved in granulosa cell tumor initiation in the SWR model. Granulosa cell tumor incidence is increased in both SWR and SWXJ-9 progenitor strains for the (SWR × SWXJ-9)F1 stock by peripubertal administration of dehydroepiandrosterone, an androgen precursor.[2, 3]

The thecal/interstitial compartment is also the source for another potential granulosa cell tumor promotive growth factor, transforming growth factor α. Transforming growth factor α is synthesized in the theca of the normal rat ovary,[16] is an epidermal growth factor–related peptide that binds to the epidermal growth factor receptor, and is implicated in tumors of several types.[17] Normal granulosa cells have a limited number of epidermal growth factor receptors, and epidermal growth factor is a modifier of gonadotropin-stimulated differentiative processes in these cells.[12] The (SWR × SWXJ-9)F1 GC tumor is characterized by elevated epidermal growth factor receptor numbers, with altered binding characteristics, and granulosa cell tumor cells show an enhanced proliferative response to this growth factor.[18] In addition to androgens and epidermal growth factor–like growth factors, other granulosa cell regulatory factors, such as transforming growth factor β, are found in thecal/interstitial cell compartment.[19]

In contrast to preneoplastic follicles, the theca is not typically a prominent feature in either primary or metastatic granulosa cell tumors of adult hosts. This suggests that if the thecal/interstitial compartment does provide a granulosa cell tumor inductive signal(s), granulosa cell tumor cell replication quickly becomes independent of this agent(s). Such a change in granulosa cell tumor cell function could be a critical step in malignant progression, and could involve an autocrine mechanism or a genetic alteration. Throughout granulosa cell tumor development, we observed small clus-

ters of loosely adherent or microfollicular granulosa cell tumor cells entering lymphatic or blood vessels. Once granulosa cell tumor cells acquired the ability to proliferate independently of thecal/interstitial cell product or other endocrine stimulation, such clusters of cells could represent a seeding mechanism for disseminating disease.

The (SWR × SWXJ-9)F1 hybrid mice have the highest incidence of spontaneous granulosa cell tumors yet encountered in our experience with the endocrine-genetic SWR model for granulosa cell tumorigenesis.[4] In addition, the frequency of tumor bilaterality in these hybrid mice was fivefold increased over that of the SWR progenitor strain.[1] This bilaterality of granulosa cell tumors appears unique because in other spontaneous rodent models[6, 7] and in other species including humans,[5] cats, dogs, sheep, cows and horses,[8, 9] granulosa cell tumors are almost always unilateral.

The high incidence, multifocal origin, and frequent bilaterality of granulosa cell tumors in this genetically defined hybrid stock suggest that the combined genome of SWR and SWXJ-9 progenitors results in maximal expression of one or more genes critical for granulosa cell tumor initiation. One gene, granulosa cell tumor susceptibility *(Gct)*, has been identified in the recombinant inbred SWXJ strains and is located on chromosome 4.[3] The (SWR × SWXJ-9)F1 mice are homozygous for the susceptible allele of *Gct*. Heterozygosity, at additional as yet unidentified loci, increases the probability for granulosa cell tumor development. Thus in a stochastic model of tumorigenesis, the (SWR × SWXJ-9)F1 mice already have a primary event encoded within their genetic complement that renders their ovaries more susceptible to subsequent tumorigenic stimuli.

In humans, two subclasses of granulosa cell tumors, juvenile and adult, have been proposed that are based on age of onset, histopathologic features, and disease progression.[5] The granulosa cell tumors found in (SWR × SWXJ-9)F1 mice resemble the human juvenile granulosa cell tumor class in several ways. In both mice and humans the majority of granulosa cell tumors arise before achievement of adult ovarian cyclicity. With respect to histopathologic features, we observed (in 42-day-old and older host mice) examples of patterns of cytology, such as hyperchromic nuclei, frequent mitotic figures, and nuclei without grooves, reported for juvenile granulosa cell tumor class.[5] We occasionally observed Call-Exner–like bodies, typical of the adult granulosa cell tumor class. Thus the predominant histologic features observed in the mouse tumors appeared more related to stage of tumor development than representative of a specific pathologic classification. Finally, with respect to disease progression, comparison is difficult because humans diagnosed with granulosa cell tumors undergo surgical intervention, whereas these mice were left untreated to ascertain malignant potential of primary granulosa cell tumors. Prediction of metastatic behavior for human granulosa cell tumors on the basis of morphologic features of the primary tumor at early stages is difficult.[5] Although the prognosis after surgical removal of the tumorous ovary for the majority of human juvenile granulosa cell tumors is very good, 5% to 10% of patients die within 2 years from widely disseminated metastatic disease.[4] These widely divergent disease outcomes suggest that there may be distinct forms of neoplasia, which cannot be easily distinguished by histologic criteria, within the juvenile granulosa cell tumor subclass. The (SWR × SWXJ-9)F1 granulosa cell tumor resembles the rapidly growing, early metastatic form of juvenile granulosa cell tumor.

In summary, the (SWR × SWXJ-9)F1 stock is characterized by a large percentage of granulosa cell tumors originating within a tightly defined developmental period attendant with puberty. Metastatic progression is significant and occurs during the young adult period. Thus these genetically defined mice provide a powerful tool for investigating mechanisms of granulosa cell tumor initiation, factors influencing primary tumor proliferation and differentiation, and changes underlying malignant disease progression. Insight gained from such studies will improve prognostic accuracy and provide rational bases for devising therapeutic methods of progressive disease management.

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Differential diagnosis between complete mole and hydropic abortus by deoxyribonucleic acid fingerprints

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We used a new method of deoxyribonucleic acid fingerprint analysis to obtain the differential diagnosis between complete mole and hydropic abortus. This method with a deoxyribonucleic acid minisatellite probe requires only a small amount of tissue sample and peripheral blood, and presents individual specific restriction fragment length polymorphisms (deoxyribonucleic acid "fingerprints") by simultaneous detection of many hypervariable regions (minisatellite regions) widely dispersed in the human genome. Southern blot hybridization showed that in cases of complete mole, all polymorphic fragments were exclusively inherited from the father. Some of the polymorphic bands of paternal deoxyribonucleic acid were not observed in molar deoxyribonucleic acid. However, in the hydropic abortus, the polymorphic fragments could be traced back to its parent. These results indicate that deoxyribonucleic acid fingerprints could distinguish the abnormal fertilization of complete mole (androgenesis) from the normal fertilization of hydropic abortus by identifying the difference in genetic variations between complete mole and hydropic abortus at the deoxyribonucleic acid level. (Am J Obstet Gynecol 1990;163:634-8.)

Key words: DNA fingerprint, minisatellite DNA probe 33.15, complete mole, hydropic abortus

Complete hydatidiform mole is a disease of trophoblasts, the layer of ectodermal tissue that attaches the embryo to the uterus. Although there are wide variations in reports on the incidence of complete mole, this tumor is the most common trophoblastic tumor throughout the world. Recent reports have indicated that the incidence of complete mole is 1 per 1200 pregnancies in United States, 1 per 500 pregnancies in Japan, and 1 per 100 pregnancies in Indonesia.[1-3] In addition to the high morbidity rate, the property of complete mole as a major risk factor to choriocarcinoma has attracted the attention of many gynecologists.[1-4]

This tumor is characterized macroscopically by a grapelike appearance that results from the accumulation of fluid in the mesenchymal core, and microscop-

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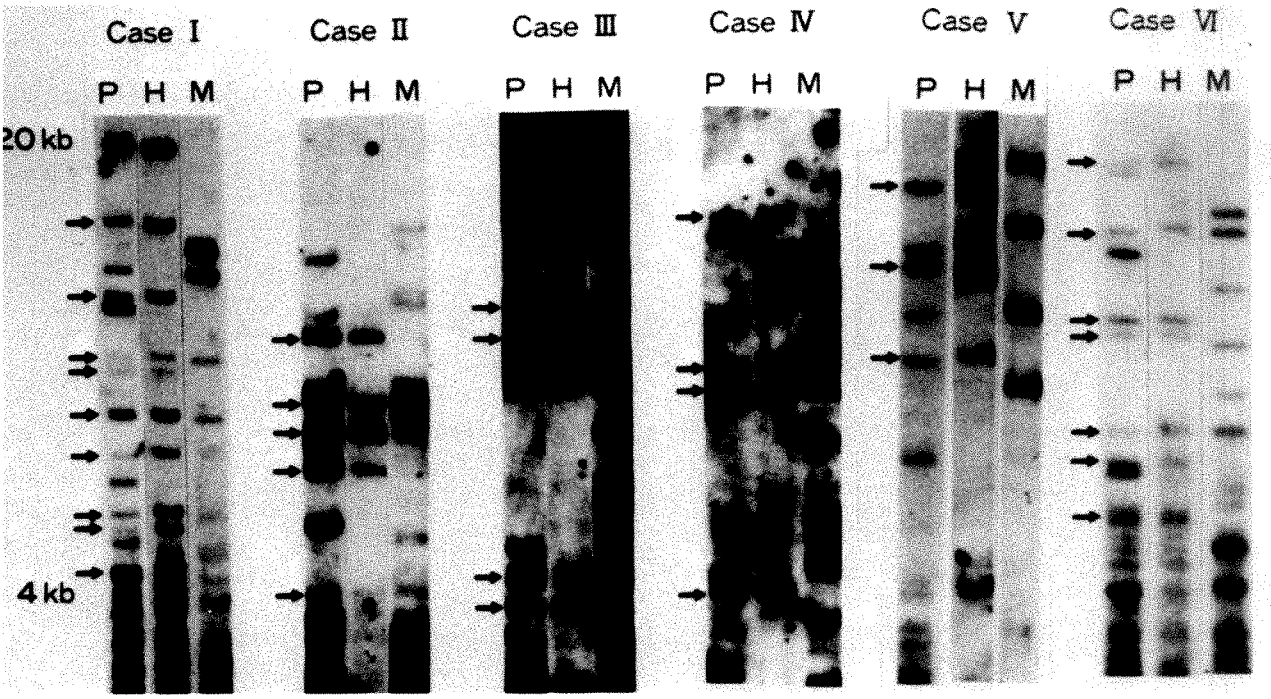


Fig. 1. The DNA fingerprints of six sets (cases I to VI) of hydatidiform molar *(H)*, paternal *(P)*, and maternal *(M)* DNA using the minisatellite DNA probe 33.15. Each polymorphic band in molar tissue can be identified as paternal in origin *(arrows)*, but some of the bands are not detected in molar tissue.

ically by trophoblastic proliferation on the villous surface. Conversely, the placental villi of spontaneous abortion frequently show hydropic change, a cystic formation of villi resembling the vesicles of complete mole. Clinically it is important to discern the hydropic abortus from complete mole because the relative risks of choriocarcinoma associated with molar pregnancy have been estimated to be 2000 to 4000 times higher than those of choriocarcinoma associated with normal pregnancy or aborted pregnancy.[5] The differential diagnosis between complete mole and hydropic abortus is generally obtained on the basis of gross and histologic findings. However, it is sometimes difficult to distinguish blighted ovum with severe hydropic changes from complete mole by histologic examination.[6]

The recent advances of recombinant deoxyribonucleic acid (DNA) technology have made it possible to characterize the genetic variations at the DNA level and revolutionalized human genetic analysis. The most prevailing method of DNA analysis is restriction fragment length polymorphisms, that is, the variation in size of restriction fragments of genomic DNA.[7] We have reported the restriction fragment length polymorphism analysis of complete mole as a new approach for the determination of androgenesis of complete mole, and showed that this method is useful for the study of the pathogenesis of the trophoblastic tumors.[8] We have shown that the differential diagnosis between complete mole and hydropic abortus can be obtained precisely by restriction fragment length polymorphism analysis with the minisatellite DNA probe 33.15, which is capable of presenting individual specific restriction fragment length polymorphisms called DNA fingerprints.[9]

Material and methods

Samples. Six molar tissues and two placental tissues with severe hydropic changes were obtained at the time of therapeutic curettage. The samples were washed repeatedly in cold phosphate-buffered saline solution, pH 7.2, and separated from maternal tissue with a pair of scissors under the dissecting microscope. In each of the six cases of moles and two cases of hydropic abortus, maternal and paternal mononuclear cells from peripheral blood samples were used for DNA extraction. High-molecular-weight DNA was extracted from molar tissues, hydropic placentas, and mononuclear cells of their parents by standard method.

Restriction enzyme digestion and DNA blotting. The extracted high-molecular-weight DNA sample (5 μg each) was digested with endonuclease *Hin*fI at 37° C for 3 hours. The digested samples were electrophoresed through a 20-cm-long 0.6% agarose gel until all DNA fragments <2 kb long had electrophoresed off the gel. After electrophoresis DNA were transferred by blotting to a nitrocellulose filter according to the

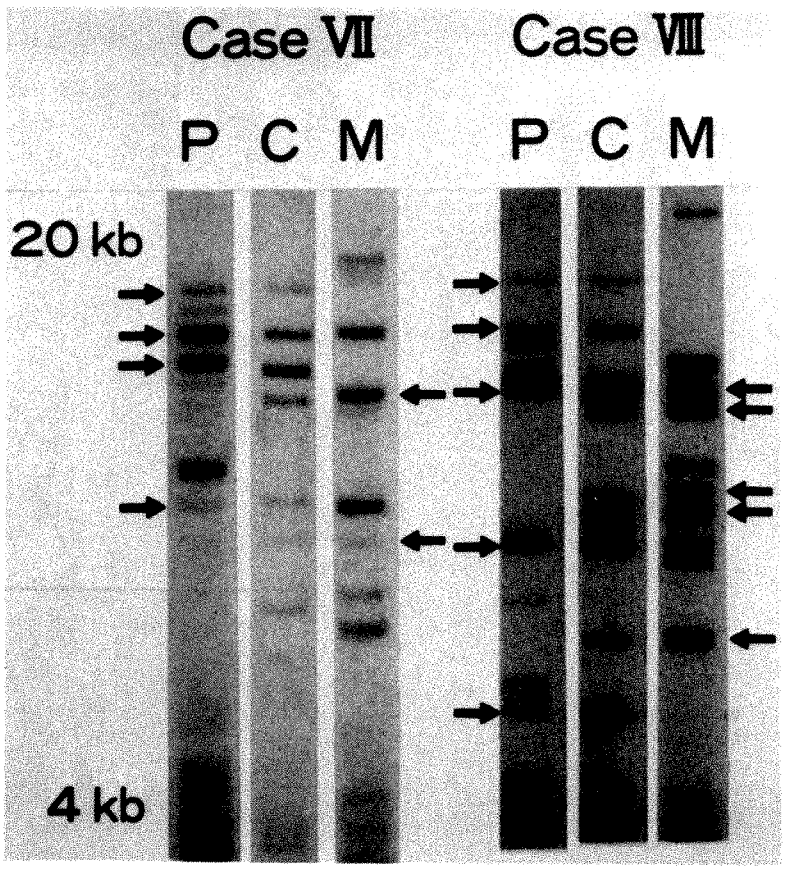


Fig. 2. The DNA fingerprints of two sets (cases VII and VIII) of hydropic chorion *(C)*, paternal *(P)*, and maternal *(M)* DNA using the minisatellite DNA probe 33.15. All bands in hydropic placenta can be traced to either parent *(arrows)*.

method of Southern.[10] The filter was baked in a vacuum oven at 80° C for 3 hours.

Hybridization and autoradiography. DNA probe 33.15, a minisatellite DNA probe, was used for restriction fragment length polymorphism analysis. (The probe was provided by Dr. Alec J. Jeffreys, University of Leicester.) The probe was labeled with phosphate 32α–deoxycytidine triphosphate by multiprime DNA labeling system (Amersham, England) to a specific activity of 1.8×10^9 cpm/μg. The ^{32}P-labeled probe was hybridized to genomic blots at 65° C for 12 hours. The hybridization was performed in Denhardt's solution, 1 mol/L sodium chloride, 50 mmol/L Tris hydrochloride (pH 7.4), 10 mmol/L ethylenediaminetetraacetic acid (EDTA), 0.1% sodium dodecyl sulfate, and 0.1% mg/ml denatured sonicated salmon sperm DNA. The filter was washed once at room temperature in 2× sodium chloride–sodium citrate and twice at 65° C in 1× sodium chloride-sodium citrate, 0.1% sodium dodecyl sulfate for 30 minutes.

Autoradiography was done with Kodak XRP-1 film (Kodak, Rochester, N.Y.) and a Lightning Plus intensifying screen (Dupont, Boston) at −80° C for 48 hours.

Results

Restriction fragment length polymorphism analysis using the minisatellite DNA probe 33.15 was performed on *Hin*fI–digested DNA of molar tissues and their parental mononuclear cells. Fig. 1 shows the profile of restriction fragment length polymorphism band patterns (DNA fingerprint) detected by probe 33.15 of six sets of complete moles and their parents. In the 4 to 20 kb size area, each individual of parents presented 10 to 20 bands that were clearly resolved, and few bands were shared among randomly selected pairs of individuals. Smaller fragments <4 kb long did not present strict individual specificity, probably a result of lower genetic variability of these loci and the fortuitous comigration of unrelated minisatellite fragments. It has been shown that these individual specific fragments >4 kb in length are unintentionally transmitted

from parents to their offspring according to Mendelian law.[9, 11] In the six cases of complete mole, however, all the bands were exclusively inherited from the fathers. Furthermore, some of the polymorphic bands in the paternal DNA fingerprint were not observed in the molar DNA fingerprint. Therefore the restriction fragment length polymorphism band pattern of mole was not identical to that of the paternal one. This phenomenon indicates the androgenetic origin of complete mole that resulted from the fertilization of an anuclear empty ovum by a single sperm that duplicates its haploid chromosomal complement or by two sperms.

In the two cases of hydropic abortus, each polymorphic fragment in the 4 to 20 kb size range of the DNA fingerprint could be traced back to its parent (Fig. 2), which suggests the parental contribution to the genome of hydropic placenta that resulted from normal fertilization.

These results indicate that even though a differential diagnosis between complete mole and hydropic abortus cannot be obtained by histologic examination, because of the severe hydropic changes of a blighted ovum, DNA fingerprint analysis could distinguish the hydropic abortus from complete mole.

Comment

Karyotype analysis has revealed that the karyotype of complete mole shows usually 46,XX, but occasionally it expresses 46,XY. Both sets of chromosomes are derived only from the father.[12] This phenomenon is explained by the fertilization of an "empty" ovum by a single X chromosome bearing sperm that duplicates its chromosomal complement[13] or by two sperms.[14] Conversely, the karyotype of conceptus, even though it presents severe hydropic change, shows 46,XX or 46,XY, and both sets of chromosomes contain parental elements. Theoretically, chromosomal marking can distinguish the hydropic abortus from complete mole. However, the karyotype analysis requires a time-consuming tissue culture (several weeks), and the analysis of chromosome banding patterns requires special techniques. Therefore this method is not suitable for the clinical laboratory. In this study we introduced a newly developed method of DNA fingerprinting to obtaining a differential diagnosis between complete mole and hydropic abortus. All the polymorphic fragments of hydropic abortus could be traced back to either parent; however, in molar tissue all the polymorphic fragments were inherited only from the father, indicating that the method of DNA fingerprinting could distinguish hydropic abortus from complete mole. The DNA fingerprint analysis has many other advantages: (1) It is a simple and more rapid method than karyotype analysis, and the results can be known within a few days. (2) The high-molecular-weight DNA for DNA fingerprint analysis can be easily extracted not only from fresh materials but also from frozen samples. (3) Less than 0.1 gm of tissue or 0.5 ml of peripheral blood can always provide sufficient DNA for analysis, and the extracted DNA can be preserved at 4° C for an extended time. (4) The DNA probe used for the restriction fragment length polymorphism analysis is directed against intranuclear DNA; thus a maternal source of DNA outside the chromosomal DNA (i.e., mitochondrial DNA of maternal origin) is excluded from contamination in this investigation. One problem with this method lies in distinguishing hydropic abortus from partial mole, another major category of hydatidiform mole. The karyotype of partial mole shows triploidy, typically 69,XXX, resulting from the fertilization of a normal haploid ovum by two normal sperms[15]; thus the polymorphic fragments in the DNA fingerprint of partial mole are transmitted from their parents as in normal pregnancy or hydropic abortus. Clinically, however, it is not important to discern hydropic abortus from partial mole because there is increasing evidence that shows that partial mole may not be associated with choriocarcinoma.[16] To the clinician it is essential to distinguish complete mole from hydropic abortus or partial mole. The DNA fingerprint is a more precise and rapid method compared with other conventional methods for the differential diagnosis of trophoblastic tumors. It is expected to contribute to the clinical management of trophoblastic tumors.

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Gestational changes in mechanical properties of skinned muscle tissues of human myometrium

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We developed a technique to obtain very thin myometrial muscle strips that allowed comparison of characteristic features of contraction from the same strip under intact and membrane-permeable ("skinned") conditions. Absolute tension development per unit of cross-sectional area induced by high potassium and oxytocin concentrations in the intact condition, or by Ca^{2+} in the skinned condition, markedly increased in human myometrium at term compared with the nonpregnant state. The maximum tension in skinned strips was 8.3 mN/mm² in nonpregnant strips and 47.5 mN/mm² at term (both obtained at 10 μmol/L Ca^{2+}). The Ca^{2+} sensitivity of the contractile proteins in skinned strips also increased at term compared with the nonpregnant state; the half-maximal response of Ca^{2+} sensitivity was 0.7 μmol/L in the nonpregnant state and 0.3 μmol/L at term. These results suggest that in human myometrium both the amount of contractile proteins and their sensitivity to Ca^{2+} may increase at term compared with the nonpregnant state. (Am J Obstet Gynecol 1990;163:638-47.)

Key words: Human myometrium, smooth muscle, skinned fiber, Ca^{2+} sensitivity, oxytocin

Uterine contractile force for expelling the fetus has been suggested to be related to increased cell volume, a rise in cell numbers or in the amount of contractile proteins in the cell, or to an increase in the efficacy of cell-to-cell connections during gestation, as estimated from biochemical, histochemical, or electrophysiologic evidence.[1, 2] According to current knowledge, calmodulin is likely to be the main Ca^{2+} receptor of the contractile proteins in smooth muscle cells, and the myosin light-chain kinase activated by the Ca^{2+}-calmodulin complex phosphorylates the myosin light chain. Myosin light-chain phosphorylation is essential for the initiation of smooth muscle contraction.[3-5] Both the activity of myosin light-chain kinase and the total amount of calmodulin in the rabbit myometrium increase during the progress of gestation.[6] Therefore the mechanical properties of myometrial cells also may change as gestation progresses. However, it is not yet clear whether these changes also occur in the human myometrium in situ.

Ca^{2+} is thought to play an essential role in contraction in smooth muscles. In myometrial cells, spontaneously generated and agonist-activated contractions are closely related to membrane activity.[2, 7] We and others recently reported that agonist-induced contractions in the rat

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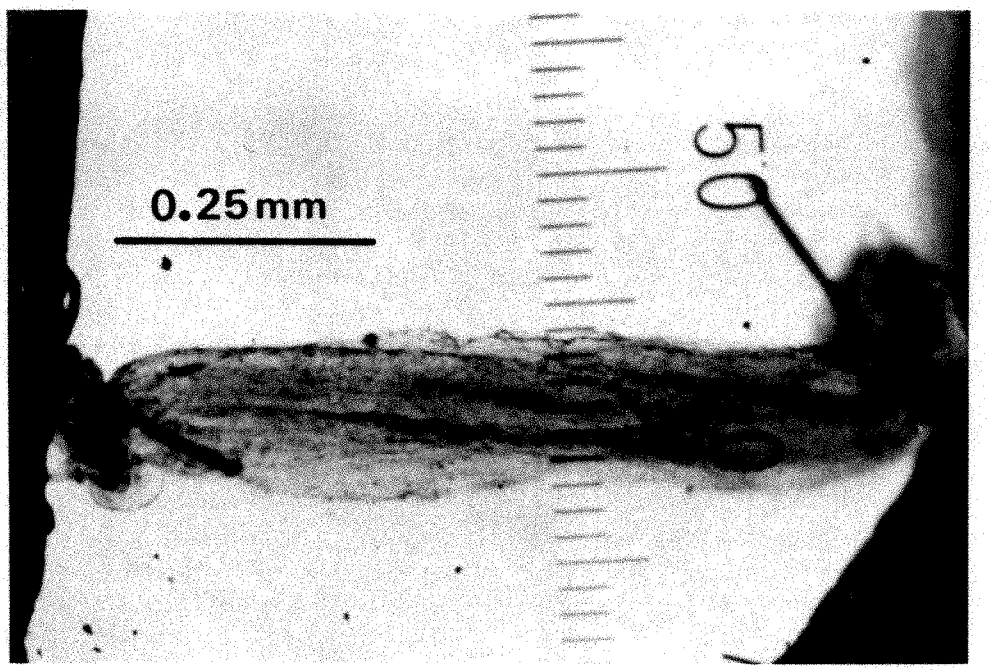


Fig. 1. Low-power light photomicrograph of a muscle fiber bundle of human myometrial strip in the experimental chamber. Small portions of the connecting silk fibers and double-sided Scotch tape are visible at each end. The knot-to-knot length was 0.80 mm, the width 0.11 mm, and the thickness 0.04 mm. Cross-sectional area was estimated to be 3.5×10^{-3} mm^2. This micrograph was taken in the relaxing solution after saponin treatment; temperature was 25° C.

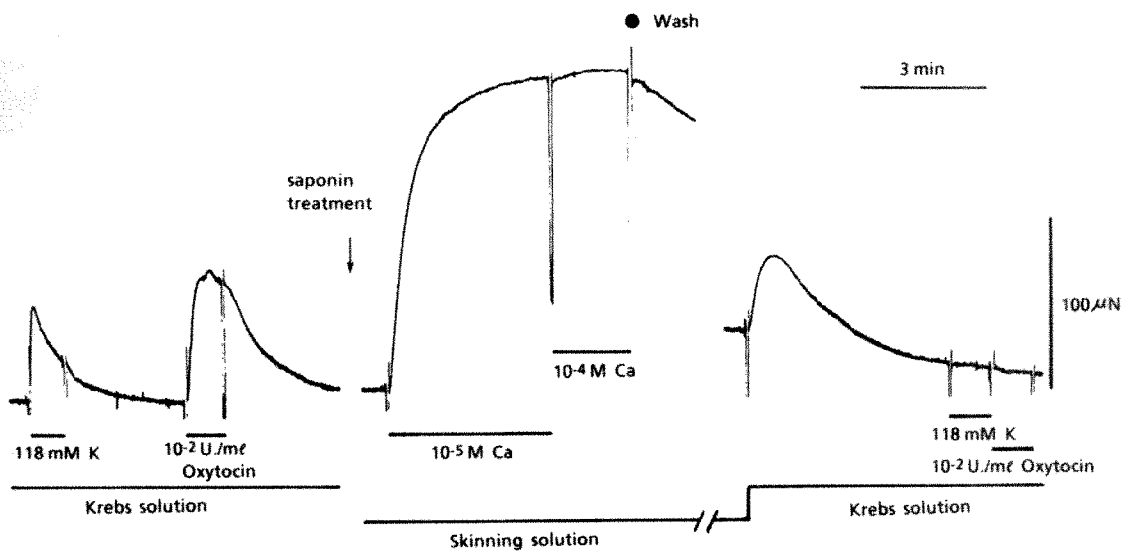


Fig. 2. Records showing criteria for the successful skinning of a muscle fiber strip of the human myometrium. First, 118 mmol/L K^+- and 10^{-2} U/ml oxytocin-induced contractions in the intact condition were recorded, then the bathing solution was replaced with relaxing solution. After saponin treatment contractions were recorded at concentrations of Ca^{2+} of 10^{-5} and 10^{-4} mol/L. Increasing the concentration of free Ca^{2+} to 10^{-4} mol/L did not change the amplitude above that produced by 10^{-5} mol/L. Finally, when the relaxing solution was replaced with modified Krebs solution for 0.5 to 1 hour, neither 118 mmol/L K^+ nor 10^{-2} U/ml oxytocin produced a contraction. When the relaxing solution was changed to the modified Krebs solution, a transient contraction was evoked. Because the modified Krebs solution has no adenosine triphosphate, the tension decay may be a result of a slow adenosine triphosphate diffusion from the strips.

myometrium use both extracellular (Ca^{2+} influx) and intracellular (Ca^{2+} release from storage sites) Ca^{2+}.[8, 9] It is plausible that changes in the contractile machinery occur during the progress of gestation.

In these experiments we attempted to clarify changes in the contractile machinery of human myometrium at term compared with the nonpregnant state. The results are discussed in relation to the gestational changes in Ca^{2+} regulation mechanisms in human myometrial cells.

Material and methods

Material. For the nonpregnant preparations, myometrial tissue was obtained from the anterior wall of the uterine corpus of six nonpregnant women who underwent hysterectomy for benign gynecologic indications (myoma, four cases; endometriosis, two cases). The mean age was 37.6 years (range, 35 to 43 years). For the pregnant at term preparations, small myometrial tissue samples were obtained from the upper incisional edge of the lower uterine segment at the time of term cesarean section with the mother under epidural anesthesia before the administration of the oxytocin (eight parous women were admitted for repeat cesarean section). The mean age was 34.3 years (range, 27 to 37 years). Both preparations were immediately placed in cold, modified Krebs solution and transported to the laboratory. Informed oral consent was obtained from the patients before tissue sampling. Myometrial strips were prepared at room temperature in modified Krebs solution during aeration with 97% oxygen and 3% carbon dioxide. To prepare the muscle strips (0.07 to 0.13 mn in width, 0.04 to 0.06 mm in thickness, and 0.7 to 0.9 mm in length), the connective tissue was carefully removed with the aid of a dissecting microscope.

Recording of mechanical responses. A muscle strip was mounted horizontally in an experimental recording chamber (capacity 0.9 ml). Both ends of the preparation were fixed with pieces of Scotch double-sided adhesive tape (3M Co., St. Paul, Minn.) and isometric tension was recorded with a strain-gauge transducer (U-gauge, Shinko, Tokyo). Width and thickness of the preparations were measured from photomicrographs with a calibrated scale, and the cross-sectional area was calculated assuming an ellipsoidal cross-section as described previously[9, 10] (Fig. 1). The test solution was applied by jetting from one end of the chamber and the solution in the chamber was siphoned from the other end. In intact muscle tissues, the maximum responses evoked by high K^+ concentration or 1×10^{-2} U/ml oxytocin were not affected by propranolol (1×10^{-6} mol/L), phentolamine (1×10^{-7} mol/L), guanethidine (1×10^{-6} mol/L), methysergide (3×10^{-7} mol/L) or mepyramine (1×10^{-6} mol/L). The maximum amplitude of contraction induced by 1×10^{-2} U/ml oxytocin was not modified in the presence of prostaglandin $F_{2\alpha}$ (1×10^{-5} mol/L) or prostaglandin E_2 (1×10^{-5} mol/L).

For the assessment of Ca^{2+} sensitivity, the tissues were skinned with saponin, according to previously described methods.[9, 11] Detailed experimental procedures for skinned muscles are described in Fig. 2. Oxytocin (10^{-2} U/ml), prostaglandin $F_{2\alpha}$ (10^{-5} mol/L), or prostaglandin E_2 (10^{-5} mol/L) had no effect on the amplitude of contraction induced by various concentrations of Ca^{2+} in saponin-treated skinned muscle strips.

The ionic composition of the modified Krebs solution was as follows: Na^+, 137.4 mmol/L; K^+, 5.9 mmol/L; Mg^{2+}, 1.2 mmol/L; Ca^{2+}, 2.6 mmol/L; HCO^{-3}, 15.5 mmol/L; H_2PO^{-4}, 1.2 mmol/L; chlorine, 134.0 mmol/L; and glucose, 11.5 mmol/L. The solution was bubbled with 97% oxygen with 3% carbon dioxide. High K^+ solution (118 mmol/L K^+) was prepared by replacing the sodium chloride with potassium chloride isosmotically; Ca^{2+}-free solution was prepared by the omission of calcium chloride from the solution and the addition of 2 mmol/L ethylene-glycol-bis-(-aminoethylether)-N,N,n′,n′-tetraacetic acid (EGTA). The pH of the solutions was 7.2. The ionic composition of the relaxing solution was: 111 mmol/L K^+-methanesulfonate, 20 mmol/L Tris maleate, 5 mmol/L Mg^{2+}-methanesulfonate, 5 mmol/L adenosine triphosphate (10 mmol/L Na^+ as Na_2ATP) and 4 mmol/L EGTA. The pH was 6.8. Solutions of various Ca^{2+} concentrations were prepared by adding appropriate amounts of Ca^{2+}-methanesulfonate to EGTA. The apparent binding constant of EGTA for Ca^{2+} was considered to be 1×10^6/mol at pH 6.8 and 25° C.[10, 11]

Drugs used in these experiments were as follows: oxytocin (for injection use; Teikoku Zoki), nicardipine (Yamanouchi), prostaglandin $F_{2\alpha}$ (Ono), prostaglandin E_2 (Ono), propranolol hydrochloride (Sigma), phentolamine (Ciba-Geigy), guanethidine sulfate (Ciba-Geigy), mepyramine maleate (May and Baker), methysergide maleate (Sandoz), saponin (ICN), adenosine triphosphate (Boehringer), EGTA (Dozin), and calmodulin (Sigma).

Where appropriate, the results obtained are expressed as the mean ± SEM. The n values represent the number of specimens. The statistical significance of the difference between mean values was assessed by Student's t test, and probability values of $p < 0.05$ were considered significant.

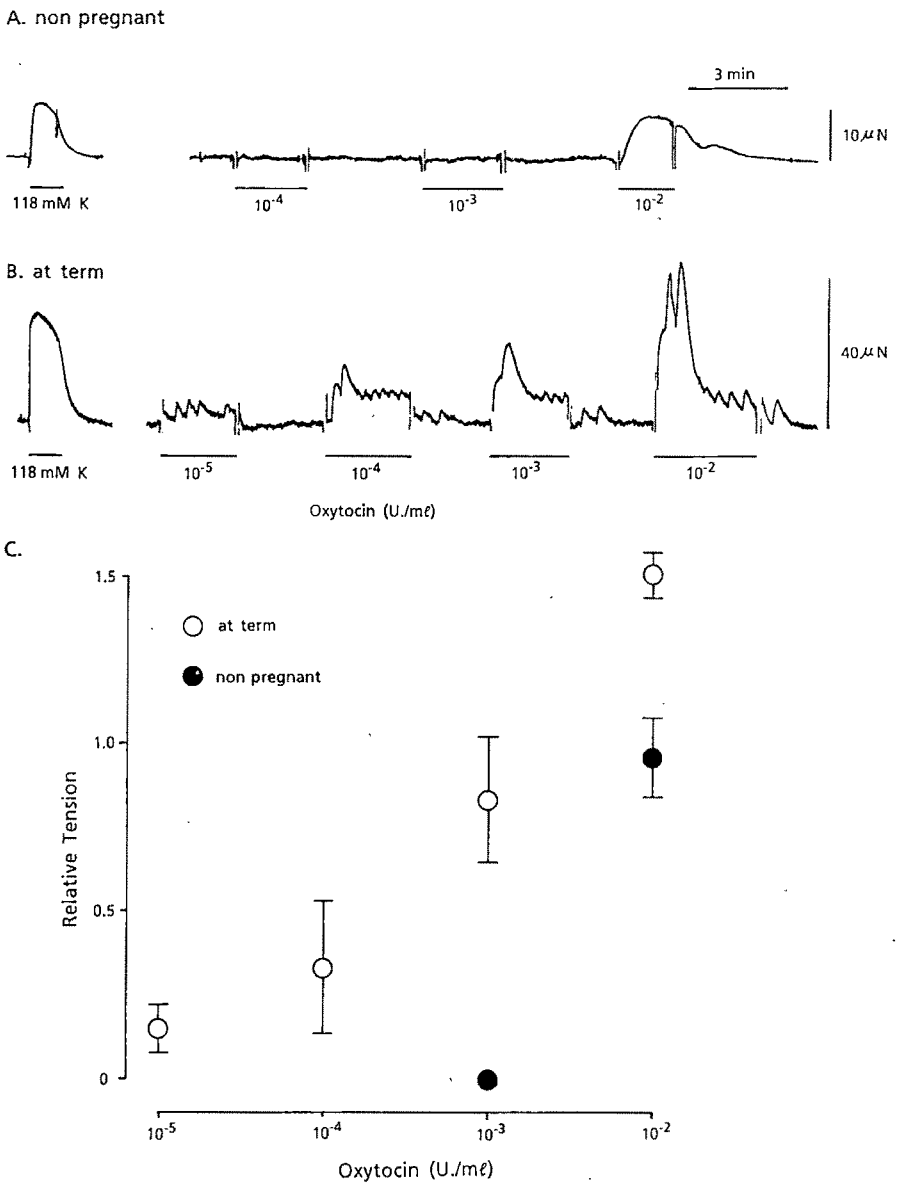


Fig. 3. Effects of 118 mmol/L K^+ concentration and various concentrations of oxytocin on the human myometrium **(A)** in the nonpregnant state and **(B)** at term. These results are typical of those from six to eight experiments. Effects of **(C)** various concentrations of oxytocin on the mechanical activity of the human myometrium when nonpregnant and at term. The amplitude of contraction induced by 118 mmol/L K^+ was normalized as 1.0 at each stage of gestation. *Solid circles,* nonpregnant; *open circles,* at term. Values represent the means; *vertical bars* indicate SEM, n = six to eight experiments.

Results

Effects of high K^+ and oxytocin on contractions of intact human myometrial strips. Thin muscle preparations (cross-sectional area between 2.2×10^{-3} mm² and 6.1×10^{-3} mm²) were obtained from human myometrium at two different stages: nonpregnant and the terminal stage of gestation. Strips prepared from either stage did not show any apparent spontaneous mechanical activity. The maximum amplitude of contraction induced by oxytocin was as great as that produced by prostaglandin $F_{2\alpha}$ but larger than that produced by prostaglandin E_2.

When a solution containing 118 mmol/L K^+ was applied, a large phasic contraction, followed by a small

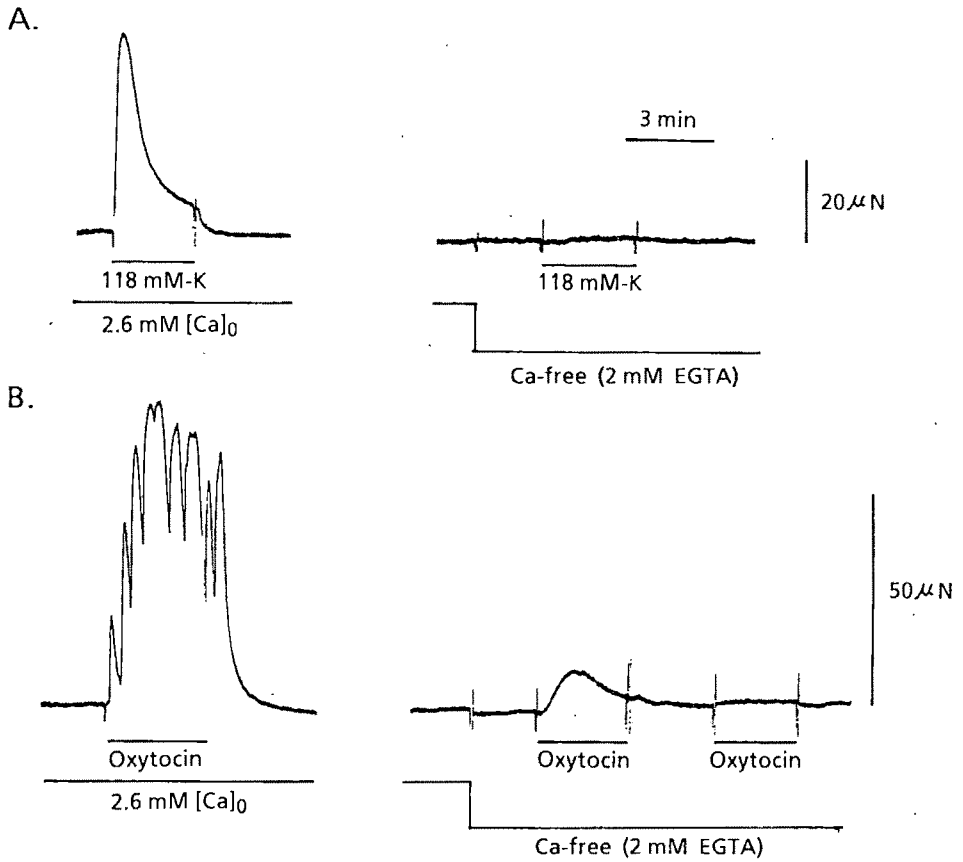


Fig. 4. Effects of **(A)** 118 mmol/L K^+ and, **(B)** 10^{-2} U/ml oxytocin in 2.6 mmol/L Ca^{2+}-containing solution and Ca^{2+}-free (2 mmol/L EGTA containing)—solution in human myometrial strips at term. These results are typical of those from eight experiments.

tonic contraction, was provoked in strips from either stage, and the shape of the contraction was almost the same in the two types of strips. Conversely, oxytocin (>10 mU/ml) induced a monophasic contraction in nonpregnant myometrial strips. However, in the strips taken at term, all concentrations of oxytocin provoked oscillatory contractions, whereas higher concentrations of oxytocin produced a phasic contraction followed by a tonic contraction on which the oscillatory contractions were superimposed (Fig. 3, *A* and *B*). Fig. 3, *C* summarizes the effects of various concentrations of oxytocin on mechanical activity in the strips taken at each stage. In nonpregnant strips the amplitude of contraction induced by 10 mU/ml oxytocin was almost the same as that induced by 118 mmol/L K^+ (0.97 times, $p > 0.1$). However, in strips taken at the terminal stage of gestation, oxytocin (10 mU/ml) produced a larger contraction than 118 mmol/L K^+ (1.51 times, $p < 0.005$). These results indicate that the sensitivity to oxytocin of the human myometrium is greatly enhanced at the end of gestation.

Effects of Ca^{2+}-free solution on contractions of intact myometrial strips induced by high K^+ or oxytocin. In Ca^{2+}-free solution containing 2 mmol/L EGTA, 10 mU/ml oxytocin, but not high K^+ concentration, produced a small transient contraction (without a tonic contraction). However, a subsequent application of oxytocin in Ca^{2+}-free solution produced no contraction (Fig. 4). These results indicate that oxytocin produces contraction via activation of Ca^{2+} influxes and via release of Ca^{2+} from the intracellular Ca^{2+} storage site(s).

Ca^{2+}-induced contraction in skinned muscle strips from human myometrium. To investigate gestational changes in the contractile proteins of human myometrium, we studied Ca^{2+}-induced contractions in chemically skinned muscle strips. To compare the amplitude of contraction in strips in the intact muscle with those of the skinned muscles, the contractions induced by 118 mmol/L K^+ and 10 mU/ml oxytocin were recorded, and the plasma membrane of the muscle strips was hyperpermeabilized by application of saponin (30

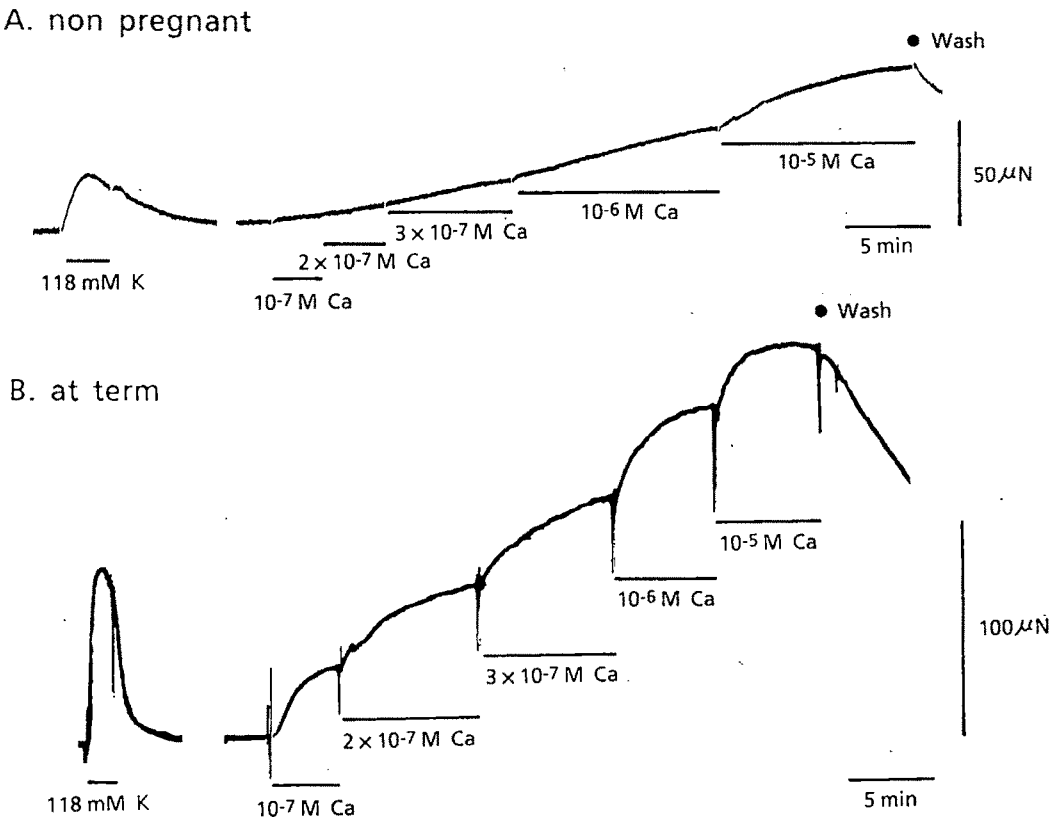


Fig. 5. Effects of various concentrations of Ca^{2+} on mechanical activity in skinned human myometrial strips when nonpregnant **(A)** and at term **(B)**. Before skinning with saponin (30 μg/ml), 118 mmol/L K^+ and 10^{-2} U/ml oxytocin were applied. After skinning the tissues, solutions containing 10^{-7} to 10^{-5} mol/L Ca^{2+} were applied cumulatively. These results are typical of those from six to eight experiments.

μg/ml) for 25 minutes in relaxing solution (thus producing "skinned" muscle strips). To minimize the deterioration of Ca^{2+}-induced contractions, various concentrations of Ca^{2+} were cumulatively applied in a stepwise manner just after the skinning procedure.[10, 11]

Fig. 5 shows the effects of various cumulatively applied concentrations of Ca^{2+} on mechanical activity in skinned strips. In strips prepared from myometrium that was nonpregnant or at term, solutions of over 0.1 μmol/L Ca^{2+} produced contraction; the maximum contraction was obtained by application of 10 μmol/L Ca^{2+}. Greater concentrations of Ca^{2+} (up to 0.1 mmol/L) did not further increase the amplitude. The tension gradually decreased after removal of Ca^{2+}. The maximum amplitude of contraction induced by Ca^{2+} in skinned strips was consistently larger than that induced by high K^+ concentration or oxytocin in intact strips whether from the nonpregnant state or the term stage of gestation ($p < 0.01$).

Fig. 6 shows the plotted data of Ca^{2+}-induced contraction. The median effective dose values were 0.66 ± 0.02 μmol/L Ca^{2+} in nonpregnant strips and 0.28 ± 0.02 μmol/L Ca^{2+} at the terminal stage of gestation ($n = 6$ to 8, mean ± SEM). The pCa tension curve obtained from the term strips was shifted to the left in comparison with that observed for the nonpregnant strips. These results indicate that contractile proteins underwent an increase in Ca^{2+} sensitivity during gestation.

To compare the amplitude of contraction produced in strips taken at the two different stages, the maximum amplitude of contraction was expressed as tension per cross-sectional area (see Methods). The tension induced by 118 mmol/L K^+ or 10 mU/ml oxytocin in strips at the terminal stage of gestation was larger than in nonpregnant strips (4.3 times with use of high K^+ solution and 6.4 times for oxytocin; $p < 0.005$). When the maximum Ca^{2+}-induced tension in skinned strips was compared at the two different stages, the strips at term generated 5.7 times the tension produced by those obtained at the nonpregnant stage ($p < 0.005$) (Fig. 7).

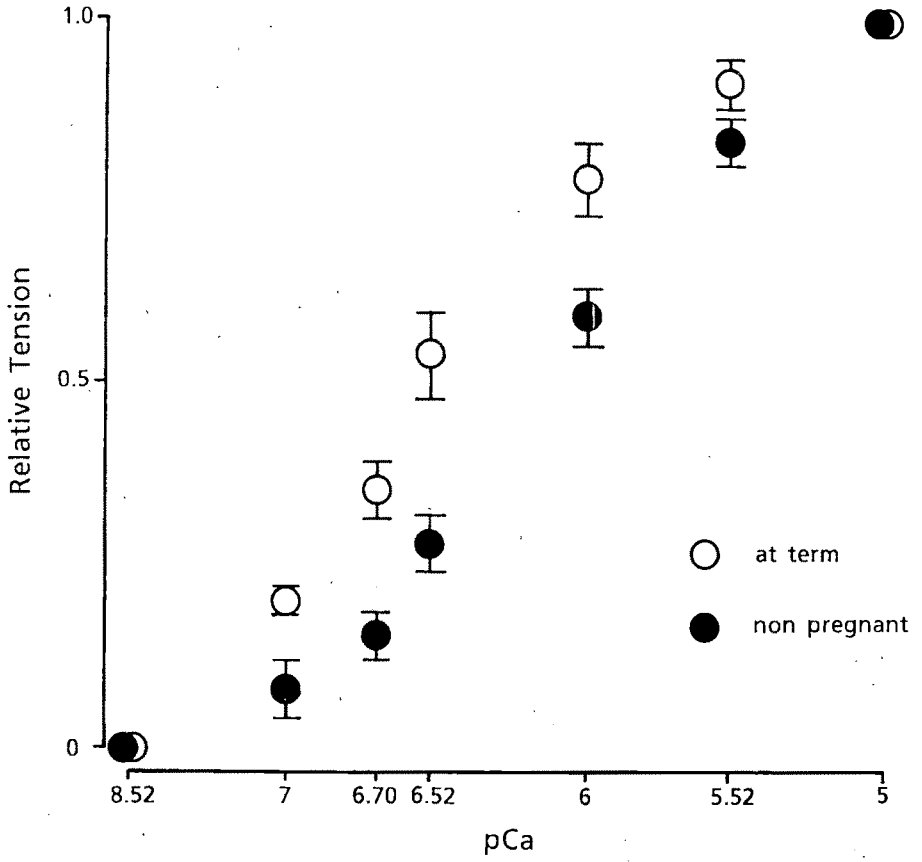


Fig. 6. The pCa-tension relationships observed in skinned human myometrial strips. The contractions are expressed in relation to the size of the contraction induced by 10^{-5} mol/L Ca^{2+} for each state; *solid circles,* nonpregnant; *open circles,* at term. Values represent the means; *vertical bars* indicate SEM, n = six to eight experiments.

The contractions induced by 118 mmol/L K^+ or 10 mU/ml oxytocin in intact strips were compared with the contractions induced by various concentration of Ca^{2+} in the same strips after skinning. The free Ca^{2+} concentrations required to evoke the 118 mmol/L K^+-induced contraction or the 10 mU/ml oxytocin-induced contraction were estimated from the pCa-tension curve for each stage of gestation. The estimated free Ca^{2+} concentrations induced by 118 mmol/L K^+ were 0.35 ± 0.03 μmol/L in the nonpregnant myometrium and 0.22 ± 0.03 μmol/L at term. Those induced by 10 mU/ml oxytocin were 0.33 ± 0.02 μmol/L for the nonpregnant myometrium and 0.29 ± 0.03 μmol/L at term (Fig. 8). These data suggest that the increase in free Ca^{2+} concentration induced by high K^+ or oxytocin in myometrium at term is of lesser magnitude than in the nonpregnant myometrium.

Comment

Our principal findings are as follows: (1) tension per unit of cross-sectional area evoked by high K^+ concentration or oxytocin in living strips, and the maximum Ca^{2+}-induced tension in skinned strips increased during gestation, (2) Ca^{2+} sensitivity of the contractile proteins measured in skinned myometrial strips was increased at the terminal stage of gestation, and (3) the minimum concentration of oxytocin required to produce a contraction was lower in strips from the terminal stage of gestation than in those from the nonpregnant stage.

The absolute tension developed per unit of cross-sectional area evoked by stimulants in intact strips was markedly increased at the end of gestation. The same effect was observed on Ca^{2+}-induced contractions in skinned strips when the intracellular ionic environment was artificially modified. Thus the increase in tension development at the terminal stage of gestation is not caused solely by changes in the plasma membrane ionic permeability (to Na^+, K^+, Ca^{2+}, or Cl^-) or by the increased density or number of oxytocin receptors.

Calmodulin is a Ca^{2+} receptor of contractile proteins, and the Ca^{2+}-calmodulin complex initiates contraction

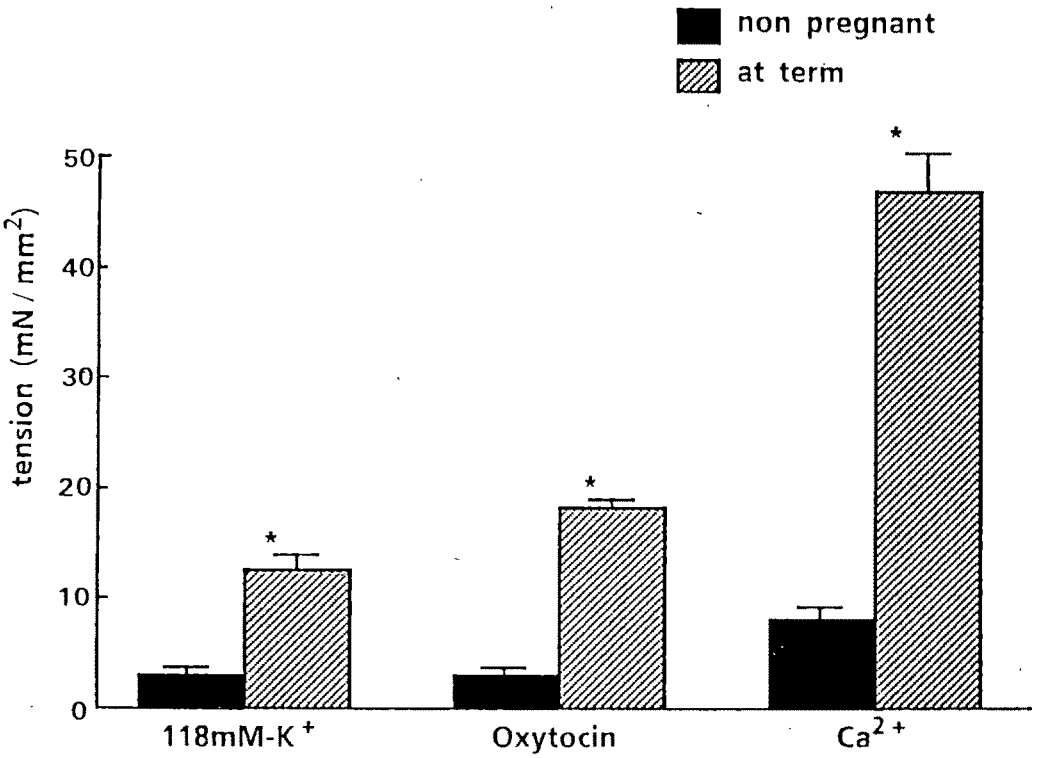


Fig. 7. The tension induced by 118 mmol/L K^+ or by 10^{-2} U/ml oxytocin in intact strips from the nonpregnant myometrium *(solid columns)* and at term *(hatched columns)*. Also shown is the maximum tension induced by Ca^{2+} in skinned strips. The tension is expressed in mN/mm^2. Values are means with bars indicating SEM, n = six to eight experiments. *Asterisks* represent significant differences between mean values for nonpregnant and term states.

by myosin phosphorylation via activation of myosin light-chain kinase in smooth muscle cells.[3-5] Matsui et al.[6] reported that both the amount of calmodulin and the activity of myosin light-chain kinase per milligram of tissue are increased during gestation in the rabbit myometrium. These results suggest that increases both in the amount of contractile proteins and of calmodulin could explain the observed increases in Ca^{2+} sensitivity of the contractile proteins and the maximum Ca^{2+}-induced contraction in skinned strips of human myometrium. However, this needs to be clarified in an intact single cell of the human myometrium.

In these experiments the concentration of oxytocin required to produce the maximum contraction was higher in our myometrial strips than other species. However, the minimum concentration of oxytocin required to produce a contraction in the myometrium at term was much less than in the nonpregnant state. In addition, Edwards et al.[12] reported that oxytocin at low concentration (0.1 mU/ml) increased the frequency of spontaneous contractions and at high concentration (1 mU/ml to 10 mU/ml) induced tonic responses with superimposed small phasic tension. This was not observed on the nonpregnant uterus.

In Ca^{2+}-free solution oxytocin produced only a phasic contraction. Thus Ca^{2+} release from the intracellular storage site(s) may occur in human myometrial strips from the terminal stage of gestation. Recently it was reported that hormones and neurotransmitters synthesize inositol-1,4,5-trisphosphate (IP_3) through hydrolysis of phosphatidyl inositol-4,5-bisphosphate, and that IP_3 releases Ca^{2+} from the sarcoplasmic reticulum.[13] Moreover, IP_3 produces contraction caused by the release of Ca^{2+} in the skinned myometrium of the pregnant rat.[14] In the myometrium the volumes of sarcoplasmic reticulum (possible candidates for the intracellular Ca^{2+} storage sites) increase during gestation.[15] We previously reported that the acetylcholine-induced contraction in Ca^{2+}-free solution was enhanced in rat myometrium with the progress of gestation.[9] It has been shown that oxytocin in the myometrium generates IP_3 and that IP_3 causes calcium release from uterine microsoma.[16,17] Nevertheless, IP_3-sensitive Ca^{2+} release mechanisms may contribute to the increased sensitivity to oxytocin of the mechanical activity of myometrial tissue at the terminal stage of gestation, although such an increase could result from an increase in the number of oxytocin receptors.

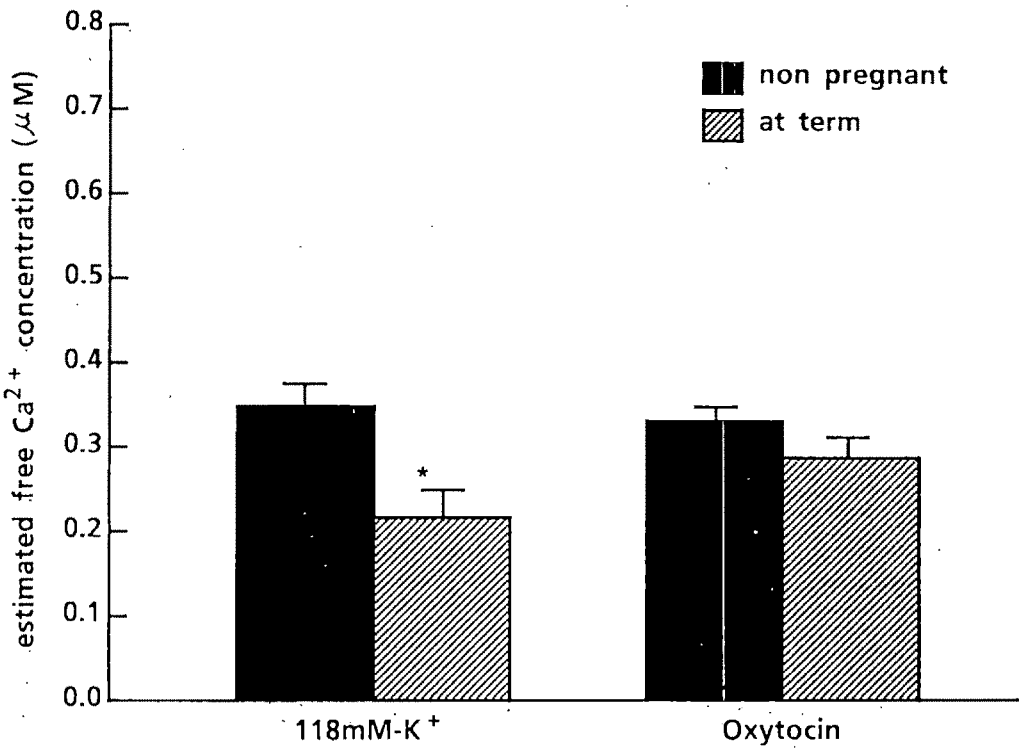


Fig. 8. The estimated free Ca^{2+} concentration required for the contraction induced by 118 mmol/L K^+ or 10^{-2} U/ml oxytocin in human myometrial strips taken from nonpregnant subjects *(solid columns)* and at term *(hatched columns)*. Values represent the means; *vertical bars* indicate SEM, n = six to eight experiments. *Asterisks* denote significant differences between means for nonpregnant and term states.

Our data suggest that the increase in the free Ca^{2+} concentration induced by oxytocin or high K^+ concentration is of lesser magnitude at term than in the nonpregnant human myometrium. Thus a smaller amount of free Ca^{2+} can produce a larger contraction in the myometrium as gestation progresses. Because the Ca^{2+} sensitivity of contractile proteins is higher in strips at the terminal stage of gestation, it may be that Ca^{2+}-handling mechanisms in the cell (such as Ca^{2+} reuptake to the storage sites or Ca^{2+}-extrusion mechanisms via the Ca^{2+} pump or Na^+-Ca^{2+} exchange on the plasma membrane) more effectively regulate Ca^{2+} concentration as gestation progresses. As a consequence cellular Ca^{2+} concentration may be maintained at a lower level and may more rapidly decline after stimulation. Because the amplitude of contraction induced by oxytocin was larger than that induced by high K^+ concentration at the terminal stage of gestation, the voltage-independent Ca^{2+} influx and Ca^{2+} release mechanism from the storage site may become more important at this time.

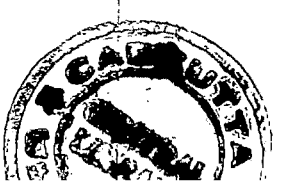
In conclusion, in the human myometrium at term the maximum amplitude of contraction induced by oxytocin is greatly increased compared with the nonpregnant state. This may be predominantly a result of increases in both the amount of its contractile proteins and its Ca^{2+} sensitivity. Roles that may be played by the Ca^{2+} storage sites in the oxytocin-induced contraction are also suggested.

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Alteration of 24-hour rhythms in myometrial activity in the chronically catheterized pregnant rhesus monkey after a 6-hour shift in the light-dark cycle

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We determined the effect of a 6-hour phase shift in the light-dark cycle on the 24-hour rhythm of myometrial activity with 15 chronically catheterized pregnant rhesus monkeys during the last third of gestation. Monkeys were housed indoors in constant temperature on a 14-hour-light/10-hour-dark photoperiod in two groups based on the time the lights were turned on (group A lights on at 6 AM and group B lights on at midnight). The power spectra were calculated for periods of 512 readings (1.138 hours) starting at the time the lights were turned on for continuous periods of 25.03 hours of data showing well-developed contraction-type activity at any time during that period. The power spectra data for contractures and contractions were analyzed separately from myometrial electromyographic data. During the 14 hours of light, myometrial activity was primarily composed of contractures. In all experimental animals the switch from contractures to contractions occurred around the time the lights were turned off. The proportion of contraction-type activity in each 1.138-hour analysis interval expressed as a percentage of the total contraction power for the whole 25.03-hour analysis period for all monkeys increased around the time the lights were turned off in both groups. The increase in contractions was observed 12 to 15 hours after the lights were turned on. No systematic change in the proportion of contracture activity was observed. Peak contraction activity was 22.6 ± 0.60 hours (16.6 hours after lights on), and was at 18.3 ± 1.4 hours (18.31 hours after lights on) in groups A and B, respectively. This difference was statistically significant (22.6 ± 0.6 vs 18.3 ± 1.4 hours, $p < 0.05$). Seven of eight monkeys in group A and six of seven in group B had switched from contractures to contractions before lights were turned off. We have confirmed a 24-hour rhythm in myometrial activity in the pregnant rhesus monkey and provided new evidence to support the endogenous nature of this rhythm and its direct relationship to the light-dark cycle (AM J OBSTET GYNECOL 1990;163:648-54.)

Key words: Myometrial activity, circadian, monkey, phase shift, pregnancy

In nonhuman primates the existence of a 24-hour rhythm in uterine activity is well documented.[1-5] However, data from different laboratories differ in the time of maximal uterine activity. Harbert[2] reported a diurnal rhythm in the chaired pregnant rhesus monkey in which maximum integrated intrauterine pressure occurred between 2:08 PM and 6:33 PM, when the lights were turned off at 4 PM. In a second report, maximal integrated intrauterine pressure occurred between 10:16 AM and 12:54 AM during the 36 hours before delivery, also with the time of lights off at 4 PM.[3] In contrast, Ducsay et al.[4] reported a nocturnal maximum in the rhythm in intrauterine pressure in the chaired pregnant rhesus monkey. Maximum hourly integrated intrauterine pressure, analyzed as the ratio between the total area under the intrauterine pressure curve per hour divided by the overall mean for the 24-hour recording period, occurred at midnight. In these studies the lights were turned off at 11 PM. Electromyographic recordings of uterine activity at three different times of the day in chaired cynomolgus monkeys showed that under conditions of natural lighting, the frequency of electromyographic events was higher between 8 PM and 9 PM compared with 4 AM to 5 AM and noon to 1 PM.[6] The first report on a 24-hour rhythm in myometrial activity in chaired pregnant rhesus monkeys with continuous myometrial electromyographic recording described a nocturnal increase in the frequency of contraction-type myometrial activity.

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6/1/21124

Contractions, when observed, occurred around the time lights were turned off (7 PM) with the highest amplitude at midnight.[5]

In all studies to date in the pregnant monkey, regardless of whether the maximum uterine activity was present during the hours of light or darkness, increased activity was always present around the time that lights were turned off. Catecholamines,[1] estrogens,[7, 8] oxytocin,[9, 10] and dehydroepiandrosterone sulfate[7] are all putative factors capable of driving the 24-hour rhythm in uterine activity, either directly or indirectly. We have been particularly interested in this transition period during which contracture-type myometrial activity changes to contractions. In the pregnant rhesus monkey this change occurs under several conditions, such as after operation,[6] before delivery,[6] during food withdrawal,[11] and when estrogen synthesis is increased by infusion of androstenedione into the mother.[8] In this study we sought to determine the effect of a 6-hour shift in the light-dark cycle on the change from contractures to contractions.

Material and methods

Fifteen pregnant rhesus monkeys of known gestational age were acclimated to the laboratory conditions as previously described.[5, 11, 12] Before the pregnancy under study, the animals usually were housed indoors with a 12 hour light/12 hour dark light-dark cycle with lights on at 6 AM at the primate center. In our laboratory they were housed in rooms with controlled light cycles 14:10 hours light-dark for at least 30 days before operation. The light intensity changed from 484 lux during the lights-on period to 5 lux during the dark period. No animal had the photoperiod changed or shifted during the stay in the laboratory. Food provided was Purina 5045 Monkey Chow (Ralston Purina, St. Louis) and fresh fruits presented to the animals every day at 8 AM (biscuits and fruit) and at 1 PM (fruit only). Monkeys had access to water during the entire experimental period. At operation monkeys ranged from 83 to 112 days gestational age. All animals were instrumented with techniques described previously in detail.[5, 11, 12] Briefly, with the animals under halothane anesthesia, catheters were placed in the maternal dorsal aorta and inferior vena cava via the femoral artery and vein. In each animal two pairs of myometrial electromyographic leads were sewn into the myometrium on the anterior wall of the uterus. Two catheters made of Tygon microbore tubing (Norton Performance Plastics, Akron, Ohio) (inner diameter, 1.27 mm; outer diameter, 2.29 mm) with a side hole 1 cm from the tip, were placed 3 to 6 cm within the amniotic cavity. A small prefabricated Tygon retaining collar around the catheter was located just within the uterus. A Yellow Spring 44032 thermistor (Yellow Springs Instrument Co., Yellow Springs, Ohio) was sutured to the anterior uterine wall. The day of operation was considered day 0. All animals but one received 75 μg buprenorphine for analgesia twice a day for the first two postoperative days. All animals were maintained on a 14-hour light/10-hour-darkness regimen. The animals were studied in two groups based on the onset of the 14 hours of light in their light-dark cycle. Animals in group A were housed in rooms with lights on at 6 AM and off at 8 PM from the day they arrived at the laboratory. Because we wished to conduct further experiments in which we would sample mother and fetus around the time lights were turned off, we changed the lighting regimen by 6 hours so the time the lights were turned off was more convenient for laboratory personnel. Animals in group B were housed in rooms with lights on at midnight and off at 2 PM from the day they arrived at the laboratory.

Recording of myometrial electromyogram and data storage. The uterine electromyogram was recorded from multistranded bipolar stainless steel wires (Cooner AS 632, Cooner Wire Co., Chatsworth, Calif.) implanted 3 to 5 mm apart on at least two sites of the myometrium.[5, 12] Acquisition of the myometrial electromyogram was performed with a computer-based data acquisition system.[13] Briefly, the electromyographic signals were sampled at 32 Hz and the average value over 8 seconds was digitized and stored as one data point reading with a time signal.

Determination of power spectrum frequency windows that characterize contractions and contractures. Fast Fourier Transform and power spectrum analysis were performed on the digitized electromyographic data with an Asyst 2.0 program.[14] We have previously demonstrated that the 0.01 to 0.11 cycles/min frequency window represents a component of uterine activity that has a low frequency (i.e., greater than one epoch of activity every 9 minutes) and correlated well with instances in which only contracture-type activity was present. The second frequency window (0.2 to 0.8 cycles/min) represents the contraction-type uterine activity. To quantify the changes in activity in each of the windows, we integrated the area under each window and defined total contraction power and total contracture power. If the area in the 0.2 to 0.8 cycles/min frequency window increases at any given period, it means that the animal had more contraction-type uterine activity than the previous period.[14]

Data analysis. Each analysis period began when the lights were turned on. Uterine electromyographic data were selected from individual monkeys with continuous periods of 25.03 hours of uninterrupted data showing well-developed contraction-type activity at any time during that period. Monkeys were 2 to 30 days after operation and 94 to 125 days of gestation on the days the recordings were used for analysis. Data were avail-

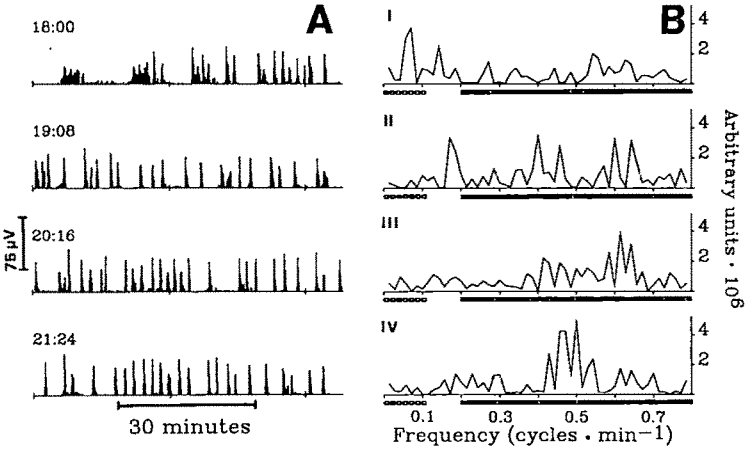


Fig. 1. A, Continuous electromyographic data for 4.33 hours (clock time indicated) and **B,** power spectrum for the data in **A** at *(I)* 6 PM to 7:08 PM (18:00 to 19:08); *(II)* 7:08 PM to 8:16 PM (19:08 to 20:16); *(III)* 8:16 PM to 9:24 PM (20:16 to 21:24), and *(IV)* 9:24 PM to 10:32 PM (21:24 to 22:32) in a pregnant rhesus monkey at 110 days' gestation housed in a room with lights off at 8 PM. *Heavy solid line,* contraction window; *broken line,* contracture window.

Table I. Details of experimental preparation

Monkey	*Gestational age at operation*	*Day 1*	*Day 2*
Group A			
1	96	107	108
2	93	124	125
3	103	107	108
4	97	102	103
5	100	102	108
6	90	120	122
7	90	106	—
8	106	109	110
Group B			
9	94	115	116
10	95	107	108
11	83	112	113
12	88	98	99
13	112	119	120
14	100	115	—
15	87	94	98

able on 2 days from thirteen and on 1 day in two animals (Table I). The power spectra for frequencies between 0.01 and 0.8 cycles/min were calculated for periods of 512 8-second readings (1.138 hours) starting at the time the lights were turned on. Twenty-two data points were obtained, covering a continuous period of 25.03 hours. The power spectra data for contractures and contractions were analyzed separately. Each analysis interval (1.138 hours) was expressed as a fraction of the total activity during the total analysis period (25.03 hours).

Statistical analysis. Data for the area of increased activity were fitted to a normal distribution in individual animals. Mean time at peak activity and its confidence interval in either group were computed. The two-sample *t* test was used to compare mean time at peak activity between the two groups. To determine whether a monkey had already switched from contractures to contractions before the lights were turned off, the mean time of the peaks minus 1.96 SDs (2.5th percentile) was calculated in each animal. If the time value for the 2.5th percentile occurred earlier than the time lights went off (8 PM for group A or 2 PM for group B), the monkey's contraction activity was considered to have anticipated the time lights were turned off. In those animals with two days of suitable recording the data were averaged for that animal before analysis. Data throughout are presented as the mean ± SD.

Results

During the 14 hours of light, uterine activity was mostly primarily of contractures. In all experimental animals the change from contractures to contractions occurred around the time the lights were turned off. Data shown in Figs. 1 to 4 focus on the two time windows 6 PM to 10:33 PM (group A) and noon to 5:33 PM (group B). These windows include the time the light went off in each group. Figs. 1 and 2 show the raw electromyographic and power spectrum analysis data for one animal from each group. In monkey no. 8 housed in a 14-hour-light/10-hour-dark photoperiod with lights off at 8 PM, uterine activity between 6 PM and 10:33 PM showed a switch from contractures to contractions in both the raw electromyographic and the power spectra for frequencies between 0.01 and 0.8 cycles/min (Fig. 1). In contrast, monkey no. 9 housed in a 14-hour-light/10-hour-dark photoperiod with lights off at 2 PM showed only contracture-type activity

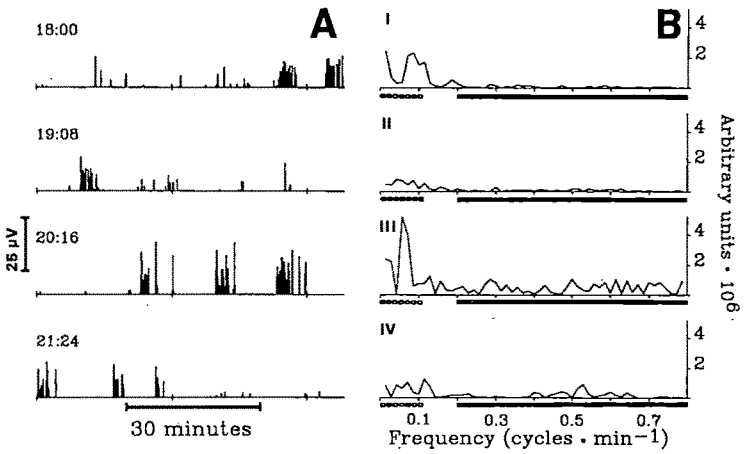


Fig. 2. A, Continuous electromyographic recording data for 4.33 hours (clock time indicated) and **B,** power spectrum for the data in **A** at *(I)* 6 PM to 7:08 PM (18:00 to 19:08); *(II)* 7:08 PM to 8:16 PM (19:08 to 20:16); *(III)* 8:16 PM to 9:24 PM (20:16 to 21:24); and *(IV)* 9:24 PM to 10:32 PM (21:24 to 22:32) in a pregnant rhesus monkey at 115 days' gestation housed in a room with lights off at 2 PM. *Heavy solid line,* Contraction window; *broken line,* contracture window.

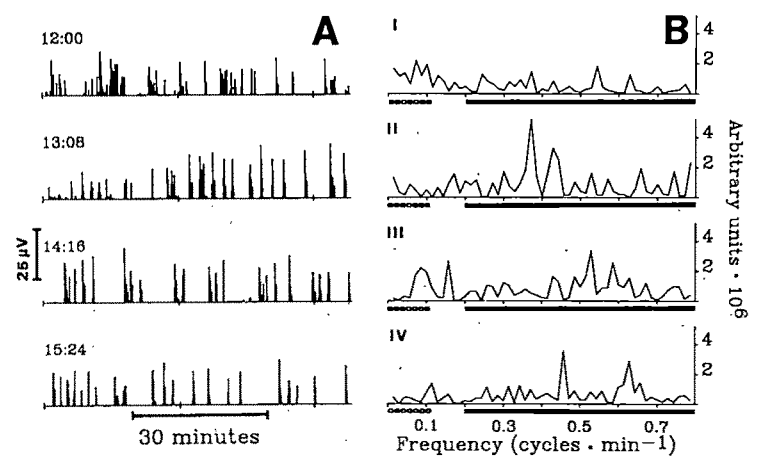


Fig. 3. A, Continuous electromyographic recording data for 4.33 hours (clock time indicated) and **B,** power spectrum for the data in **A** at *(I)* noon to 1:08 PM (12:00 to 13:08); *(II)* 1:08 PM to 2:16 PM (13:08 to 14:16); *(III)* 2:16 PM to 3:24 PM (14:16 to 15:24); and *(IV)* 3:24 PM to 4:32 PM (15:24 to 16:32) in a pregnant rhesus monkey at 115 days' gestation housed in a room with lights off at 2 PM. *Heavy solid line,* Contraction window; *broken line,* contracture window.

in the 6 PM to 10:33 PM time window (Fig. 2). In monkey no. 9 uterine activity between noon and 4:33 PM showed a switch from contractures to contractions (Fig. 3), whereas monkey no. 8 showed only contracture-type activity in the noon to 4:33 PM time window (Fig. 4.) in both the raw electromyographic data and the power spectrum.

The proportion of contraction-type activity in each 1.138-hour analysis interval expressed as a percentage of the total contraction power for the entire 25.03-hour analysis period for all monkeys increased around the time the lights went off. The increase was observed 12 to 15 hours after the lights were turned on for both group A (Fig. 5, *A*) and group B (Fig. 6, *A*). No systemic change in the proportion of contracture activity throughout the 25.03-hour period was observed in either group (Fig. 5, *B* and 6, *B*).

Table II shows the mean time of peak activity calculated as the peak value of the fitted normal distribution on individual animals. Mean time of peak activity for animals in group A was at 22.55 ± 0.60 hour (clock time) that corresponds to 16.56 hour after lights went on. The confidence interval was 22.04 to 23.06. Mean time of peak activity for animals in group B was at 18.31 ± 1.39 hour (clock time) that corresponds to 18.31 hours after lights went on. The confidence in-

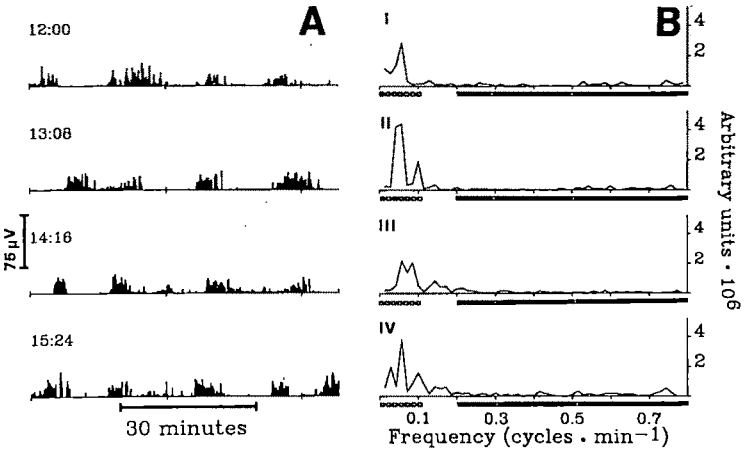


Fig. 4. A, Continuous electromyographic recording data for 4.33 hours (clock time indicated) and **B,** power spectrum for the data in **A** at *(I)* noon to 1:08 PM (12:00 to 13:08); *(II)* 1:08 PM to 2:16 PM (13:08 to 14:16); *(III)* 2:16 PM to 3:24 PM (14:16 to 15:24); and *(IV)* 3:24 PM to 4:32 PM (15:24 to 16:32) in a pregnant rhesus monkey at 110 days' gestation housed in a room with lights off at 8 PM. *Heavy solid line,* Contraction window; *broken line,* contracture window.

terval was 16.88 to 19.41. The mean time at peak activity between groups A and B was statistically different (22.55 ± 0.60 versus 18.31 ± 1.39 hours; $p < 0.05$, two-sample t test), when clock time is used, and they are not different (16.56 ± 0.6 versus 18.31 ± 1.39) when time relative to lights on is used.

As shown in Table II the majority of animals in both groups had a 2.5th percentile time value less than the time at which lights were turned off. Seven of eight monkeys started their increased activity before 8 PM in group A and six of seven displayed contractions before 2 PM in group B. Thus most animals had already switched from contractures to contractions before the lights were turned off.

Comment

Mammalian biologic rhythms are driven by an endogenous oscillator that is constantly adjusted to the environment by entrainment based on external cues.

The goal of the study was to determine the effect of a 6-hour shift in the light/dark cycle on the 24-hour rhythm of myometrial activity. The results enable us to exclude feeding time and cleaning time as possible exogenous conditioning stimuli driving this rhythm. Feeding and cleaning occurred at the same clock time irrespective of whether animals belonged to group A and group B. However, the change from contractures to contractions occurred at the same time in relation to the time lights were turned off.

Our data suggest that the 24-hour myometrial rhythm is entrained rather than driven by the change in light intensity (from lights on to off) because no animal showed a change from contractures to contractions at the exact time lights were turned off. Thirteen of the fifteen animals studied showed a switch from contractures to contractions that anticipated the time the lights went off. Anticipation is a characteristic of endogenous rhythms when entrained by an external cue. Environmental temperature does not affect the period of circadian rhythms, but it can act as a zeitgeber under natural conditions.[15] Temperature is kept constant under our laboratory conditions and can therefore be ruled out as a zeitgeber in our studies.

These data confirm previous reports from our laboratory and others that the myometrium in the pregnant rhesus monkey is most active during the early hours of darkness. Although different methodologies were used by the different research groups, all studies show the highest activity around the time lights were turned off. Some activity always occurred before the lights went off.

With an oxytocin antagonist we have shown that oxytocin plays a role in the switch from contractures to contractions under certain conditions.[10] However, the exact mechanism by which oxytocin may operate has not been determined. A 24-hour rhythm in oxytocin plasma concentration is one possible mechanism that may explain a 24-hour rhythm in myometrial activity.

Changes in the sensitivity of the myometrium to oxytocin throughout the 24-hour day is another possible pathway by which oxytocin may determine the rhythm in myometrial activity. We have shown that the myometrium is more sensitive to oxytocin when administered in the early hours of darkness in pregnant monkeys at 121 to 142 days' gestation housed in a 14-hours-light/10-hours-dark cycle.[9]

The involvement of steroids in the control of myometrial activity has been suggested by several studies.[4, 7, 8] Increased maternal plasma estrogen concentrations induced by food withdrawal[7] or 48-hour

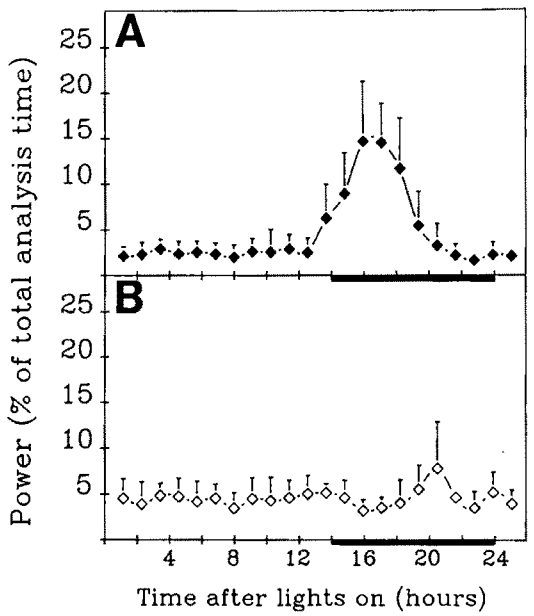


Fig. 5. Power in the contractions **(A)** and contracture **(B)** power spectrum windows in each analysis interval (1.138 hours) expressed as a percentage of the total activity in that window for the full analysis period (25.03 hours) in eight monkeys housed in 14-hours-lights/10-hours-dark photoperiod with lights off at 8 PM (mean ± SD). *Heavy solid line* indicates the period of lights off during the analysis period.

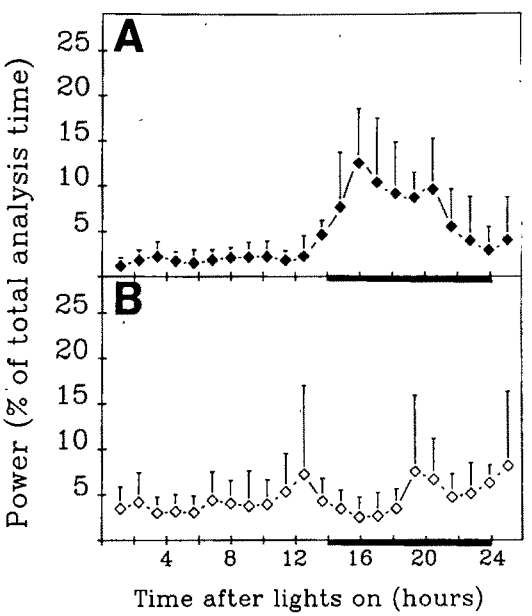


Fig. 6. Power in the contractions **(A)** and contracture **(B)** power spectrum windows in each analysis period (1.138 hours) expressed as a percentage of the total activity in that window for the full analysis period (25.03 hours) in seven monkeys housed in 14-hours-light/10-hours-dark photoperiod with lights off at 2 PM (mean ± SD). *Heavy solid line* indicates the period of lights off during the analysis period.

Table II. Start time increased myometrial activity derived as the time at which the contraction window power was 1.96 SD before the mean and peak activity time of increased myometrial activity

	Group A		*Group B*	
Monkey no.	*Start time*	*Peak activity time*	*Start time*	*Peak activity time*
1	19.33	23.43	11.30	16.76
2	17.33	22.19	12.25	17.68
3	18.36	22.23	15.12	20.68
4	19.47	22.63	13.17	19.00
5	18.88	22.69	13.18	18.32
6	20.27	23.38	12.83	16.78
7	18.21	21.81	12.97	18.93
8	18.58	21.95	—	—
Mean	18.80	22.55	12.87	18.31
±SD	± 0.89	± 0.60	± 1.15	± 1.39

intravenous administration of the estrogen precursor 4-androstenedione[8] is associated with the appearance of contractions during the dark period. Fetal plasma dehydroepiandrosterone sulfate concentration is highest at the time of increased myometrial activity.[16] Whether dehydroepiandrosterone truly drives the rhythm or whether plasma concentration changes are purely coincidental has not been established. Fetal dehydroepiandrosterone could affect myometrial activity by providing a source of estrogen precursors to the placenta. Plasma catecholamines have also been suggested to play an important role in the regulation of the 24-hour rhythm in myometrial activity. Harbert and Zuspan[1] have shown a correlation between urinary catecholamine excretion and increased myometrial activity in the nonpregnant monkey. In contrast, no correlation between plasma or amniotic catecholamine concentrations and the cycles of myometrial activity was found in the pregnant rhesus monkey late in gestation (Ducsay CA. Personal communication).

In conclusion, we have confirmed the presence of a 24-hour rhythm in myometrial activity in the pregnant rhesus monkey and provided new evidence to support the endogenous nature of this rhythm and the direct relationship to the light-dark cycle. Future studies involving constant illumination are required to determine the exact role and nature of the cues provided by the light-dark cycle.

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Nifedipine enhances the cardiac toxicity of magnesium sulfate in the isolated perfused Sprague-Dawley rat heart

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Magnesium sulfate is commonly used in tocolytic regimens and as prophylaxis against seizures. Nifedipine may be used simultaneously in either situation. With the isolated perfused rat heart model (Sprague-Dawley rats), we investigated the effects of these agents on cardiac function. Whereas each agent alone depressed cardiac performance, the two drugs together had maximal depressive effects on the heart. (AM J OBSTET GYNECOL 1990;163:655-6.)

Key words: Nifedipine, magnesium sulfate, tocolysis

Preterm labor and preeclampsia complicate a significant number of pregnancies. Magnesium sulfate, commonly used as a tocolytic agent, is the agent of choice for seizure prophylaxis in the preeclamptic patient. Recently nifedipine, which is a calcium channel agonist, has been added to tocolytic[1] and antihypertensive[2] regimens. Occasionally a patient is simultaneously exposed to magnesium sulfate and nifedipine. Each agent alone is known to have a depressive effect on myocardial function.[3,4] We investigated the interaction of magnesium sulfate and nifedipine in the isolated perfused rat heart.

Methods

This project was approved by the Committee on Animal Research at the University of North Carolina. All care and procedures were within committee guidelines. Thirty Sprague-Dawley rats were anticoagulated with 1000 units of heparin intraperitoneally and anesthesized with ether. The heart of each rat was then rapidly excised, arrested in ice saline solution (0.9%), and attached to a modified Langendorff apparatus. The isolated hearts were perfused with Krebs-Henseleit solution. The solution was aerated with 95% oxygen and 5% carbon dioxide. The perfusate entering and surrounding the heart was warmed by a water-jacketed system to 37° C.

A miniature latex balloon-tipped catheter filled with saline solution (0.9%) was inserted into the left ventricle through the mitral valve to measure cardiac dynamics. Left ventricular systolic pressure was continuously measured. Left ventricular end-diastolic pressure was maintained at 6 mm Hg. Contractility (dP/dt) was determined from the slope of the left ventricular pressure waveform. Atrial and ventricular surface electrodes were placed and heart rate was also recorded. Myocardial cells are viable for at least 90 minutes in Krebs-Henseleit solution.

The hearts were randomized into three groups after 15 minutes of stabilization in the Krebs-Henseleit solution. A set of baseline measurements were obtained. At that time the 10 hearts in group 1 had the magnesium concentration increased from 2.4 mEq/L to 6.4 mEq/L, group 2 had nifedipine added to the perfusate at a rate of 2 ng/min, and group 3 had the magnesium concentration increased to 6.4 mEq/L and nifedipine added. After 10 minutes in the new solution another set of measurements were obtained.

Mean values were obtained from each group at the first and second observations. Means were compared with a Student t test and an analysis of variance where appropriate; $p < 0.05$ was considered significant.

Results

Baseline heart rate, left ventricular systolic pressure, and contractility did not differ between the three groups. The addition of magnesium in group 1 significantly reduced heart rate ($p < 0.03$), left ventricular systolic pressure ($p < 0.0001$), and contractility ($p < 0.00002$). Group 2 had an insignificant decline in mean heart rate and significant diminution of left ventricular systolic pressure ($p < 0.00002$) and contractility ($p < 0.000001$). The hearts in group 3 showed significant declines in heart rate ($p < 0.02$), left ventricular systolic pressure ($p < 0.000001$), and contractility ($p < 0.000001$) (Table I). Overall changes between groups were compared by calculation of the percent

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Table I. Comparison of mean cardiovascular parameters before and after intervention

	*HR-1**	*HR-2†*	*p Value*	*LVSP-1‡*	*LVSP-2§*	*p Value*	$\frac{dP}{dt}$*-1‖*	$\frac{dP}{dt}$*-2¶*	*p Value*
Group 1	262.5	217.1	0.03	92.6	60.4	0.0001	2004.3	1089.8	0.00002
Group 2	261.7	244.6	—	99.8	61.1	0.00002	1994.6	953.6	0.000001
Group 3	259.6	207.0	0.02	97.6	43.6	0.000001	1958.3	544.6	0.000001

*Heart rate in beats per minute at first observation.

†Heart rate in beats per minute at second observation.

‡Left ventricular systolic pressure in millimeters of mercury at first observation.

§Left ventricular systolic pressure in millimeters of mercury at second observation.

‖Contractility in millimeters of mercury per second at first observation.

¶Contractility in millimeters of mercury per second at second observation.

Table II. Percent change in cardiovascular parameters after intervention (mean ± SD)

	Group 1	*Group 2*	*Group 3*
Heart rate	−17 ± 16	−4 ± 7	−18 ± 15
Left ventricular systolic pressure	−35 ± 8	−37 ± 10	−56 ± 12
Contractility	−46 ± 14	−51 ± 12	−73 ± 8

of change in each measurement after drug administration (Table II). The combination of nifedipine and magnesium sulfate produced a larger decrease in left ventricular systolic pressure than did either agent alone ($p < 0.001$). The combination of the two agents also produced a greater percent of decrease in contractility than that of either magnesium sulfate or nifedipine alone ($p < 0.001$).

Comment

Both magnesium sulfate and nifedipine given alone depressed left ventricular systolic pressure and contractility within this model. Nifedipine seemed to reduce heart rate less than did magnesium sulfate. Combining the two agents resulted in more depression of left ventricular systolic pressure and contractility compared with either drug alone. In the modified Langendorff apparatus, nifedipine does potentiate the depressive effects of magnesium sulfate.

Overlack et al. observed a depressive effect on blood pressure when these two agents were combined. The Overlack study found that animals receiving oral supplements of magnesium showed an increased hypotensive effect when given nifedipine.[5]

A recent case report is supportive of the concept that magnesium potentiates the cardiac depressive effects of nifedipine. Waisman et al. reported on two patients who had magnesium infused for preeclampsia while receiving oral nifedipine; both patients had marked hypotension.[6] A similar case on our service in a gravid woman who underwent tocolysis with each agent prompted us to initiate this study.

Nifedipine and magnesium sulfate were potent cardiovascular depressants when combined in this particular model. The isolated Langendorff preparation is without vascular and neural reflexes and attenuation of the depressive effects of these agents may occur in the intact animal when compensatory mechanisms are present. However, we urge the clinician who considers combined use of these agents to proceed with caution.

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Effect of intravaginal application of prostaglandin E_2 gel on the mechanical properties of the ovine cervix uteri at term

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The extensibility ("creep" or strain per minute) and the stretch modulus (stress per unit strain) of strips of cervical tissue were measured in vitro. Intravaginal application of prostaglandin E_2 gel led to a fourfold increase in the extensibility (mean ± SE, 15.45 ± 0.26 versus 4.23 ± 0.86 min^{-1}; $p < 0.05$) and a twofold reduction in the stretch modulus (mean ± SE, 0.66 ± 0.03 versus 1.28 ± 0.12 $N \cdot mm^2$; $p < 0.0005$). This marked increase in the degree of softening occurred in the absence of an increase in uterine activity or changes in plasma progesterone concentrations. (Am J Obstet Gynecol 1990;163:657-60.)

Key words: Cervix, extensibility, stretch modulus, softening, prostaglandin E_2

Parturition requires a soft distensible cervix to allow expulsion of the fetus. Cervical ripening is essential if dilatation is to be achieved without damage to the maternal soft tissues or to the fetus. Failure of the cervix to soften and subsequently dilate is an important cause of dystocia in sheep, as well as in human beings. However, there are anatomic differences. For example, the ovine cervix bears characteristic annular folds that virtually obliterate the lumen.

A variety of systems have been developed to measure changes in the physical properties of the cervix, including static loading of isolated cervical rings to measure extensibility,[1] intracervical balloons to measure compliance in vivo,[2-4] and tensile tests (dynamic loading) to determine stretch modulus of cervical strips.[5-8]

Parturition in sheep is preceded by a sharp rise in plasma prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) concentration,[9] which it has been suggested plays an important role in cervical softening.[10, 11] Administration of a prostaglandin synthetase inhibitor at term[8] or during labor[12] inhibits cervical softening in the sheep. There is growing evidence of a direct involvement of $PGF_{2\alpha}$ and prostaglandin E_2 (PGE_2) in cervical ripening in late pregnancy.[10, 11, 13] In human beings PGE_2 is widely used to promote clinical ripening of the unfavorable cervix.[14] The ovine cervix is capable of endogenous production of prostaglandins with the rate of production increasing during late pregnancy to reach a maximum at term,[15] and this may provide a normal mechanism of local control of cervical function.

The present investigation was designed to study objectively the direct effect of intravaginal application of PGE_2 on ovine cervical softening at term.

Material and methods

Precisely date-mated, purebred Welsh mountain ewes ($n = 10$) from a closed flock (modal gestational length = 147 days) were used. At all times procedures for the care and use of the animals conformed to the standards approved by the University of Liverpool.

Around day 130 of pregnancy, one maternal jugular vein was conventionally catheterized. At laparotomy, under halothane anesthesia, an open-tipped polyvinylchloride catheter (1.0 mm inner diameter, 2.0 mm outer diameter, Portex, England) was introduced aseptically into one allantoic sac, anchored to the uterine wall with closure sutures, then exteriorized to the flank and terminated with a three-way tap for subsequent connection to a pressure transducer. Procaine penicillin G 1.25 gm and dihydrostreptomycin 1.25 gm (Streptopen, Pitman-Moore, United Kingdom) were given intramuscularly postoperatively only once. Jugular catheters were flushed daily with heparinized (50 $U \cdot ml^{-1}$) sterile saline solution (0.9% sodium chloride). Studies were designed to end on day 140 or 145 after mating. Ewes were killed by stunning and exsanguination, and the cervix was dissected out with the use of minimum traction.

Uterine activity was monitored by connecting the open-tipped allantoic sac catheters to a physiologic pressure transducer (Bell and Howell, United Kingdom) recording on a four-channel recorder (Devices, United Kingdon). Before the start of treatment, jugular blood samples were collected daily for 2 to 3 days, then every 4 to 6 hours throughout the treatment period. Plasma concentrations of progesterone were measured

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by radioimmunoassay.[16] The sensitivity of this assay was 6.0 pg · ml^{-1}, with intraassay and interassay coefficients of variance of 9.5% and 12.5%, respectively.

For intravaginal administration of PGE_2 we used Prostin vaginal gel (Upjohn, United Kingdom) containing 1 mg dinoprost in a sterile prepacked syringe designed for use in women. The packs were stored at 4° C until use. The syringe nozzle was extended 2 cm to facilitate deposition of gel at the external cervical os. Gel was administered every 8 hours times three doses commencing day 139 (2 mg) or 144 (1 mg) ($n = 5$). Gestational age–matched ewes ($n = 5$) in which the syringe was inserted and removed at corresponding times to treated animals were used as controls.

Extensibility

*Creep testing.*Strips approximately 3 mm wide were taken from the dense connective tissue layer of the wall of the cervix and the thickness of the wall was measured microscopically as previously described.[8] The strips were held vertically by clamps (10 mm apart) in aerated (20% oxygen and 5% carbon dioxide) physiologic saline solution in an organ bath at 39° C and equilibrated for 10 minutes before longitudinally loading. A total of three similar sized strips per animals, one each from the uterine, middle, and vaginal regions of the cervix, were tested.

Each strip, effectively 10 mm long and 3 mm wide, was subjected to a static load of 0.5 N and consequential tissue extension was recorded over a period of 1 hour with a precalibrated linear displacement tracking transducer (RDP LVDT type D5/1000, RDP Electronics, United Kingdom). The transducer signal was amplified by a D7M transducer amplifier (RDP Electronics) and fed to a potentiometric recorder (Servoscribe, Smiths, United Kingdom). After initial rapid extension to its true length, each strip extended linearly with time. A straight line was fitted along this linear portion of the extension-time tracing and extrapolated to time 0. From this the initial length (L_0), the length at 1 hour (L_{60}), and the slope of the curve (K) ($K = (L_{60} - L_0)/60$) were obtained. The creep rate (extensibility), calculated with the formula $((K/L_0) \times 10{,}000)$,[5] is a measure of extension per unit length per unit time after application of a load. An increase in creep implies softening of the tissue.

Tensile testing. Tensile testing was performed as previously described.[8] Briefly, nine strips from each cervix were cyclically stretched and relaxed, at 5 mm · min^{-1}, between zero tension and 1 N, in an engineer's tensile testing machine (T5002, J. J. Lloyd Instruments, Southampton, England). The relationship of length to tension was automatically recorded on an XY-Plotter (J. J. Lloyd). A straight line was drawn along the linear portion of the extension-tension plot to determine the length at zero load (L_0). The following parameters were recorded or calculated: cross-sectional area (CSA), length at 1 N (L_{1N}), stress at 1 N (1N/CSA), strain $((L_{1N} - L_0)/L_0)$ and stretch modulus (stress/strain). Stretch modulus is derived from stress divided by strain. The lower the stretch modulus, the easier it is to stretch the tissue (softer). Stress represents tension per unit unstressed cross-sectional area after application of a known force. Strain expresses the increase in length after loading as a fraction of the original length of the specimen.

A one-way analysis of variance was performed on the data with an SPSSX 21 program on an IBM 3081 computer. Because there was no difference ($p < 0.05$) between the responses on different days (140 or 145) or at different doses of PGE_2, the data were pooled.

Results

The results (mean ± SE) of the mechanical tests performed on strips of cervical tissue are shown in Tables I and II. Intravaginal application of PGE_2 gel led to a fourfold increase in the creep rate ($p < 0.05$) and a twofold reduction in the stretch modulus ($p < 0.005$). There was a variation in the creep rate and stretch modulus along the cervix with the uterine end being most extensible.

Recorded uterine activity was negligible in the control and treated sheep: PGE_2 treatment did not stimulate uterine activity. No significant ($p < 0.05$) differences were observed in plasma progesterone concentration (mean ± SE) between the control and treatment groups either before treatment (13.0 ± 5.72 versus 10.4 ± 3.61 ng · ml^{-1}) or after treatment (12.8 ± 5.11 versus 9.8 ± 4.49 ng · ml^{-1}).

Comment

We used two methods to measure changes in the physical properties of the ovine cervix uteri after intravaginal application of PGE_2 gel. The two methods yielded similar results. Our methods allow us to compare cervical strips of a precise size and length thus minimizing variations as a result of differences in the tissue size. Multiple sampling from each cervix allows comparison of different regions of the cervix. Cervical rings in vitro have been used to measure changes in the extensibility[13] of the ovine cervix. In our experience the large size of the ovine cervix and the presence of thick annular bands of wall tissue make this technique unsuitable in the sheep because of the difficulty in preparing rings of even width and because application of traction to large rings in a consistent manner is difficult.[2, 3] Intracervical balloons have also been used in intact sheep,[3] allowing repeated compliance measurements in the same animal. However, the introduction of the balloons itself induces a transient increase in

Table I. Extensibility (creep or strain per minute) of strips of cervical tissue from control and PGE_2-treated sheep on day 140 or 145 of pregnancy

Treatment	*No. of strips*	*L_0 (mm)*	*L_{60} (mm)*	*K ($mm \cdot min^{-1}$)*	*Creep*
Control	15	12.50 ± 0.20	12.70 ± 0.25	0.016 ± 0.011	4.23 ± 0.86
PGE_2	15	15.40 ± 0.94	16.70 ± 0.70	0.024 ± 0.002	15.71 ± 2.11

Table II. The mean (±SE) stretch modulus (Newton · mm^{-2}) of strips of cervical tissue taken from control and PGE_2-treated sheep on day 140 or 145 of pregnancy

Treatment	*No. of strips*	*L_0 (mm)*	*L_{IN} (mm)*	*Slope (Newton · mm^{-1})*	*Stretch modulus*
Control	45	11.85 ± 0.45	13.20 ± 0.60	0.82 ± 0.10	1.28 ± 0.12
PGE_2	45	13.05 ± 0.35	15.05 ± 0.25	0.56 ± 0.03	0.66 ± 0.03

compliance[2] (i.e., it affects the factor it is trying to measure). Furthermore, such balloons must be placed between defined annular rings of the ovine cervix to permit comparisons between animals, but there is no reliable way to ascertain and maintain precise position.

We used our in vitro system to study the effect of intravaginal administration of PGE_2 on cervical softening. A 1.0 mg dose was chosen on the basis of extrapolation from human data.[17] Moreover, we wanted to avoid the risk of inducing contractions.[18] Intravaginal application of PGE_2 led to a marked reduction in the stretch modulus and a dramatic increase in the extensibility of ovine cervical tissue. This occurred in the absence of any significant increase in uterine activity or of change in progesterone status, suggesting local action of the hormone, which agreed with the observations of Ledger, Ellwood, and Taylor.[13] Stys et al[3] used much larger doses of PGE_2 (30 mg, compared with 3 to 6 mg in our study) and reported a tenfold increase in compliance after 20 hours. However, the regimen of Stys et al resulted in clinical labor in three of eight ewes and suggests that uterine contractions were probably initiated not only in these three but also in the other five ewes. Under such circumstances it is difficult to separate the direct prostaglandin effects on cervical softening from those as a result of uterine contractions. Our observation provides evidence for direct action of PGE_2 on softening of the ovine cervix.

We did not find any difference between the response of the sheep to PGE_2 at day 140 and 145, which suggests that the ovine cervix is responsive to the softening effect of PGE_2 by day 140 of pregnancy (i.e., a week before term). This is interesting because this response occurs before the major maternal steroid endocrine changes to which cervical softening has hitherto been attributed.

The gradation in softening along the cervix confirms our earlier report.[8] The reason for the variation is not very clear, but could be related to the distribution of collagen in the cervix. The connective tissue in the cervix is such that the uterine end has the least amount of collagen.[19, 20] Because locally administered PGE_2 is known to influence collagen and proteoglycan metabolism,[17, 21] areas with less collagen could conceivably soften faster. The variability in extensibility of the cervix seen in our study support this suggestion.

Ovine cervical tissue may be less sensitive to PGE_2 than the human cervix, as indicated by the ability of the low doses (2 to 5 mg) per vaginum or (0.5 to 1 mg) intracervically to induce within 12 to 16 hours marked improvement in the cervical state in women at term.[14, 17, 18, 21] There is need for more clinical trials in sheep of PGE_2 gel given per vaginum as a means to induce cervical softening.

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Effects of clonidine on breathing movements and electrocortical activity in the fetal lamb

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Clonidine is a recommended antihypertensive for use during pregnancy, although little is known of its fetal effects. This study examines the effects of clonidine on breathing and sleep-state cycling in fetal lambs. Clonidine was infused into a fetal lateral ventricle for up to 24 hours at 128 to 135 days' gestation. Control infusions of artificial cerebrospinal fluid had no effect. Clonidine infusion significantly reduced the incidence and episode duration of fetal breathing for the duration of the infusion period. Cycling of electrocortical activity became irregular and rapid, and the incidence of high-voltage electrocortical activity (equivalent to quiet sleep) was reduced. Fetal heart rate decreased but arterial pressure was unaffected. After infusion the breathing incidence and episode duration both increased significantly compared with control, with continuous high-amplitude breathing for several hours, whereas the incidence of high-voltage electrocortical activity remained low. Because lung development is promoted by fetal breathing, long-term use of clonidine during pregnancy could slow lung development by reducing fetal breathing activity. (AM J OBSTET GYNECOL 1990;163:661-8.)

Key words: Clonidine, fetal breathing, electrocortical activity, lung development

The α_2-adrenergic agonist clonidine is used extensively as an antihypertensive agent and has been recommended for use during pregnancy.[1] Although it has no teratogenic effects or acute toxicity, the possibility of more subtle developmental effects on the fetus has not been studied.

In adults clonidine reduces arterial pressure by acting at inhibitory presynaptic α_2-adrenergic receptors on noradrenergic neurones. This causes hyperpolarization and inhibition of firing[2-4] and leads to a reduction in sympathetic outflow and a decrease in arterial pressure. Other effects include sedation and hypothermia. Although these effects of clonidine are well known, the fetal effects of clonidine have attracted little attention. Intravascular injections of 10 μg clonidine caused an immediate arrest of fetal breathing,[5] although clonidine had no consistent effect on breathing postnatally.[6] The α_2-adrenergic antagonist idazoxan blocked the actions of clonidine, thus confirming its α_2-adrenergic action, although when given alone idazoxan had little effect on fetal breathing; presumably the α_2-adrenergic receptors were not tonically active, and thus their blockade made no difference under normal conditions. Clonidine injections also caused an immediate onset of high-voltage electrocortical activity. Breathing in the fetal lamb is normally suppressed in high-voltage electrocortical activity, but apnea and the shift to high-voltage were shown to be independently mediated since both still occurred after complete brainstem transection.

This evidence suggested that in the fetus noradrenergic facilitatory tone is required to maintain breathing, perhaps via α_1 receptors, and could be blocked by activating α_2-adrenergic receptors either exogenously with clonidine or by an endogenous neurotransmitter, probably noradrenaline. However, we examined only short-term acute effects of systemic injections of these substances and the responses seen could have been nonspecific effects of a transient high plasma concentrations.

To address this possibility and to study the effects of maintained high central concentrations of clonidine we infused clonidine into chronically prepared fetal lambs in utero for periods of up to 24 hours. Because prolonged intravascular infusions of diffusible drugs such as clonidine are likely to produce unpredictable indirect effects on the fetus via changes in the maternal circulation, the agents were administered via an indwelling cannula to a fetal lateral cerebral ventricle for periods up to 24 hours while breathing, nuchal electromyogram, electrocortical activity, arterial pressure, heart rate, and arterial blood gases were recorded.

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Table I. Effect of lateral ventricle infusion of cerebrospinal fluid on incidence and episode duration of fetal breathing and electrocortical activity

	Control	*Infusion*	*Postinfusion*
Incidence of high-voltage electrocortical activity (min/hr)	24.7 ± 3.5	22.4 ± 5.8	25.5 ± 2.1
Incidence of breathing (min/hr)	30.0 ± 4.8	29.9 ± 5.5	26.2 ± 5.1
Duration of high-voltage electrical activity episodes (min)	12.1 ± 3.2	11.1 ± 2.9	12.7 ± 2.7
Duration of breathing episodes (min)	13.8 ± 4.0	14.1 ± 3.2	12.9 ± 3.2

All comparisons between control, infusion, and postinfusion values were not significant by ranked-pairs test.

Material and methods

Experiments were performed on a total of 15 fetal lambs prepared for chronic recording using methods based on those of Boddy et al.[7] All procedures and protocols were approved by the institutional animal care and use committee. Pregnant Dorset cross ewes at between 120 and 125 days' gestation were anesthetized with intravenous Pentothal, intubated, and ventilated with oxygen and nitrous oxide 2:1 with 2% halothane. Following normal sterile methods, pairs of stainless steel wire recording electrodes were implanted in the fetal diaphragm, nuchal extensor muscle, and parietal cortex. Vinyl catheters (1 mm inner diameter) were placed in a fetal carotid artery and jugular vein and in the trachea. A fourth catheter ended in the amniotic fluid to act as a pressure reference. A lateral ventricle cannula was placed using a method based on that described by Gluckman and Parsons.[8] An acrylic guide tube was anchored to the skull at 7 mm anterior and 7 mm lateral to bregma with screws and cyanoacrylate glue. A saline-solution–filled cannula made from a 21-gauge hypodermic needle bent at right angles was introduced through the guide until it entered a lateral ventricle as shown by the fall in the saline solution column. The cannula was then glued in place in the guide. Vinyl tubing (0.25 mm inner diameter × 1 m) was attached to the exposed end of the cannula via an adapter tube and secured with cyanoacrylate glue. Dead space of catheter and cannula combined was about 100 μl. The uterus was closed in two layers and catheters and electrodes were exteriorized through a flank incision. Recovery from anesthesia was rapid and the ewes usually stood and fed within an hour of skin closure.

Three days were allowed to elapse from the time of operation before any experiments were performed. An infusion rate of 33 μl/hr was used throughout the study. Drugs were made up in artificial cerebrospinal fluid, adjusted if necessary to pH 6.5 to 7 with carbon dioxide, and sterilized by passage through a 0.22 μm filter. Clonidine was made up at 250 μg/ml and infused at 33 μl/hr (dose rate of 8.3 μg/hr). Preliminary studies indicate that clonidine is stable in solution with no apparent change in potency over several days. In control studies artificial cerebrospinal fluid was infused at the same rate. (See Appendix for composition.) Fetal electrocortical activity, integrated diaphragm and nuchal electromyograms, tracheal and arterial pressures, and heart rate were recorded continuously on Grass polygraphs.

Data were analyzed from the chart recordings manually. For each preparation steady-state measurements were made of the 10 hours before infusion started ("control"), the infusion period starting 4 hours from the start of infusion and continuing to the end ("infusion"), and the 10-hour period starting with the end of the infusion period ("postinfusion"). Mean heart rates and arterial pressures were measured from the traces twice hourly during control, infusion, and postinfusion periods. In each consecutive 2-hour epoch of these periods, the incidence of fetal breathing and high-voltage electrocortical activity were measured in minutes per hour, and the duration of each episode of breathing and high-voltage electrocortical activity measured. No attempt was made to quantify either low- or intermediate-voltage electrocortical activity. All data were entered into spreadsheets (Lotus 1-2-3) for collation, plotting, and statistical analysis. Blood gas samples were obtained during control, infusion, and postinfusion steady-state conditions.

Frequency distributions of some of the data, particularly breathing incidence, were truncated by zero and were therefore clearly nonnormal. Such data cannot be treated by standard parametric statistics and were therefore tested with a nonparametric test (Wilcoxon for unpaired and ranked-pairs test for paired data), and medians are used in these cases instead of means.

Results

Artificial cerebrospinal fluid infusions. Recordings from 11 infusions of artificial cerebrospinal fluid in 11 preparations were analyzed. There were no significant differences between values for control, infusion, and postinfusion on breathing or electrocortical activity (Table I). No effects of infusion on heart rate, arterial

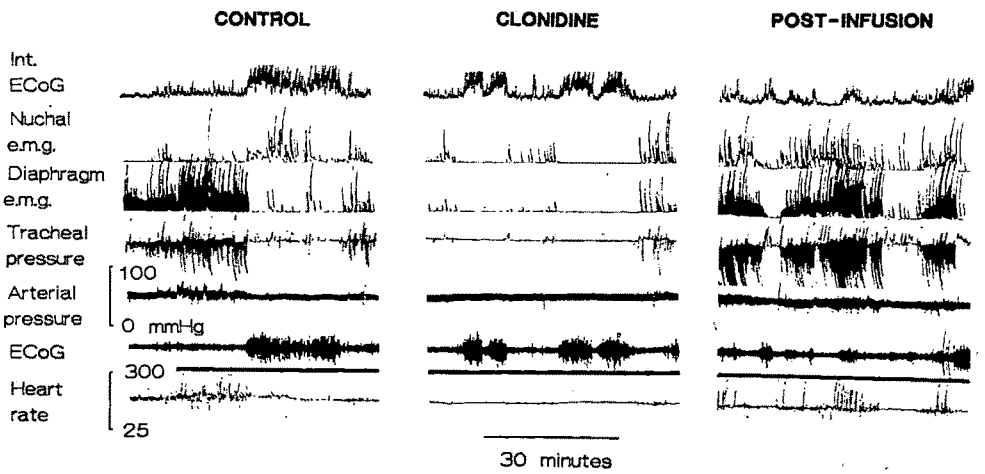


Fig. 1. Typical recordings from a 128-day fetal lamb before, during, and after infusion of clonidine via intraventricular catheter at 9 μg/hr. Vertical and horizontal ordinates apply to all three panels. During clonidine infusion both heart rate and blood pressure show low variability, and diaphragm and nuchal activity are reduced. After infusion episodes of intense diaphragm and nuchal activity occur together and the incidence of high-voltage electrocortical activity remains low compared with control.

Table II. Fetal ascending aortic pH and blood gases under control conditions, during central clonidine infusions, and during recovery

	pH	Pco_2 *(mm Hg)*	Po_2 *(mm Hg)*	*n*
Control	7.443 ± 0.081	42.99 ± 5.29	23.61 ± 4.41	22
Clonidine	7.442 ± 0.061	41.50 ± 4.92	27.15 ± 4.52	7
Recovery	7.395 ± 0.040	43.25 ± 5.39	25.4 ± 4.47	11

*None of the experimental values were significantly different from corresponding control values.

pressure, or nuchal activity were detectable by inspection.

Clonidine infusions. Twenty-one infusions of clonidine at 9 μg/hr were given to 10 fetal lambs at 125 to 135 days' gestation for periods ranging from 7 to 24 hours (mean, 15.6 hours). Blood gas levels were not significantly affected by the infusions (Table II). After steady conditions had been established (maximum of 4 hours from start of infusion), infusion duration had no detectable effect and data for the remaining infusion period were pooled. Fig. 1 shows a comparison between recordings of breathing, electrocortical activity and nuchal activity, heart rate, and blood pressure in a fetal lamb under control conditions and during clonidine infusions. The reduction in electromyographic activity and increased rate of electrocortical activity cycling during clonidine infusion is clear. Both during and after infusion, nuchal and diaphragm electromyographic activity tended to occur together, whereas they were mutually exclusive in control conditions. There was increased breathing and nuchal activity during the postinfusion period. Heart rate was reduced and appeared less variable during infusion. Fig. 2 shows typical changes in incidences (*A*) and episode durations (*B*) for high-voltage electrocortical activity and breathing during a 20-hour infusion.

Breathing. Changes in the incidence (minutes per hour) and mean episode duration (minutes) of breathing episodes were measured in successive 2-hour periods. Fig. 3 shows the pooled values for breathing incidence and episode duration before, during, and after clonidine infusion for each preparation. Each preparation was its own control and comparisons were made only between data from the same preparation under different conditions. Incidence and duration were significantly reduced during infusion and increased in the postinfusion period. In all experiments the incidence decreased; the median change was −66% (range, 10% to 75%; $p = 0.00004$). Ten percent of the 2-hour periods measured showed zero breathing incidence during clonidine infusion. Duration of breathing episodes also decreased during clonidine infusions by a median of −55% (range, 19% to 79%; $p < 0.0001$) compared with control.

In the 10-hour period after infusion, both incidence and duration of breathing episodes increased signifi-

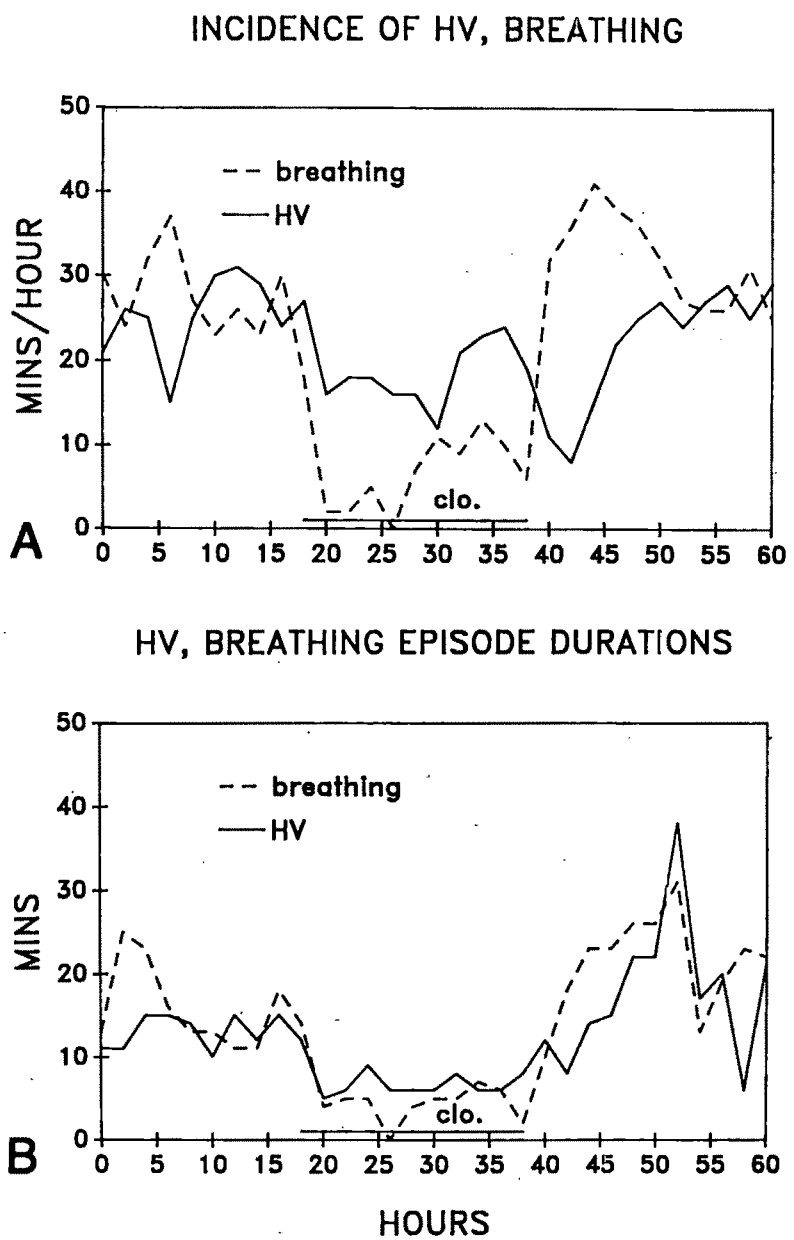


Fig. 2. Typical changes in **(A)** incidence and **(B)** episode duration for breathing and high-voltage electrocortical activity associated with a 20-hour infusion of clonidine via intraventricular catheter. Breathing incidence, episode duration, and high-voltage electrocortical activity duration were reduced during infusion and increased during recovery. High-voltage activity incidence in this case was relatively unaffected.

cantly above control. Breathing incidence increased by a median of 32% (range, 4% to 71%; $p = 0.01$) and 37% of observations showed breathing incidences of more than 40 minutes per hour in this period. Duration also increased significantly, and postinfusion breathing episodes lasting up to 4 hours occurred.

The amplitude of breathing in the postinfusion period appeared to be greater than control, and this was confirmed in one preparation in which the diaphragm electromyographic signal was processed by a quantitative (nonleaky) integrator, showing a transient twofold to threefold increase over control during the postinfusion period. The delay between the end of infusion and the onset of continuous breathing varied between less than 1 hour and more than 10 hours. During the postinfusion hyperpnea, breathing was not always confined to low-voltage electrocortical activity. Fig. 4 shows an example where breathing continued through high-

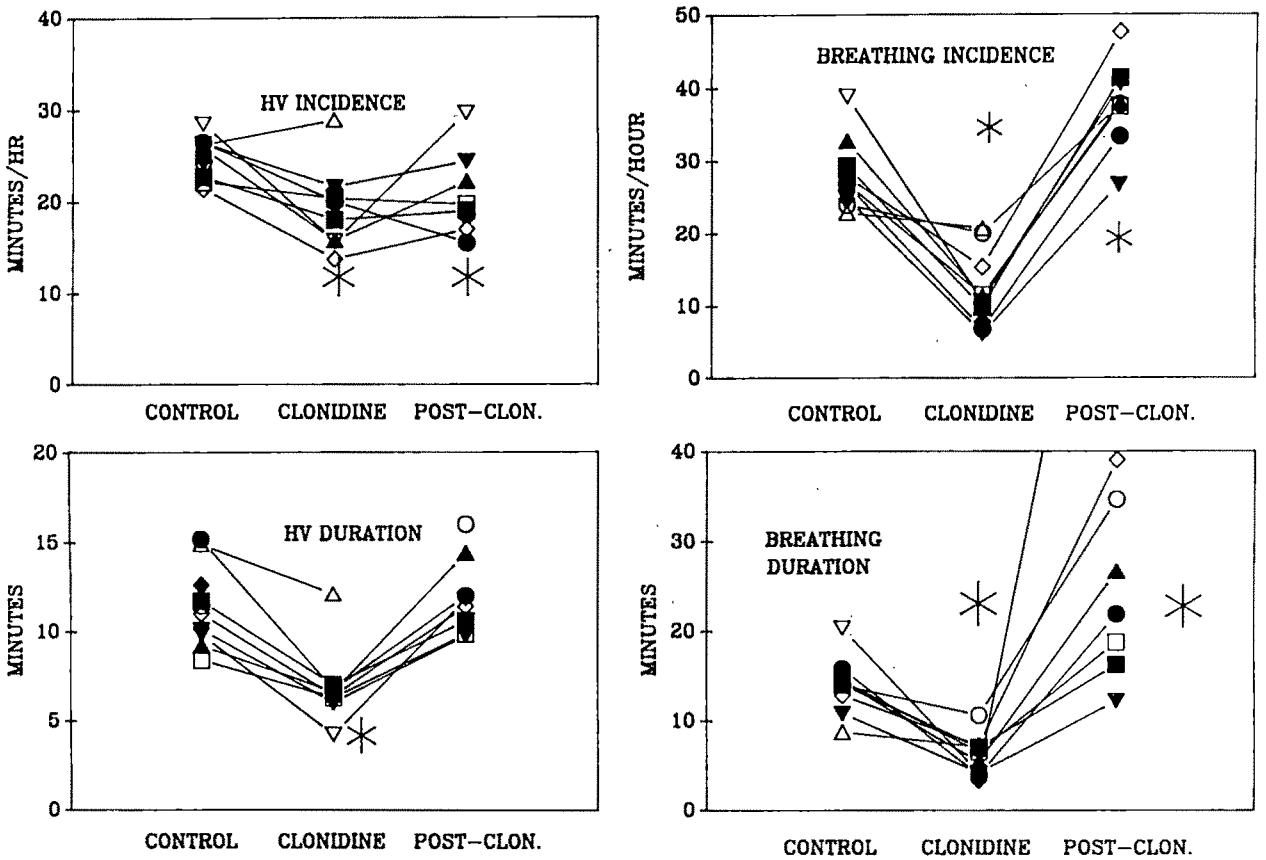


Fig. 3. Pooled values for high-voltage activity and breathing incidence and episode duration for each preparation before, during, and after clonidine infusion. The *lines* join points calculated from all data from a single preparation. Significant differences between control and experimental pooled data are indicated by *asterisks* (comparison of paired data by ranked-pairs test).

voltage electrocortical activity, during which there was nuchal activity and an increase in amplitude of breathing. This association of breathing, electrocortical, and nuchal activity is abnormal, occurring rarely if at all under control conditions.

Electrocortical activity. The incidence and episode durations of high-voltage electrocortical activity were measured over successive 2-hour periods. Fig. 3 shows the pooled values for incidence and episode duration before, during, and after clonidine infusion for each preparation. Significant differences from control ($p < 0.05$ by ranked-pairs test) are shown by asterisks. Each preparation was its own control and comparisons were made only within preparations. Clonidine significantly reduced both the incidence and duration of high-voltage electrocortical activity. The incidence of high-voltage activity decreased in all but one preparation; the median change was −26% (range, +10% to −46%, $p < 0.005$). After clonidine infusion the incidence of high-voltage electrocortical activity increased, but over the 10-hour postinfusion period values were still significantly below control (median change of −11%, range +4% to −41%; $p = 0.04$).

High-voltage electrocortical activity episode duration decreased in all preparations during infusion by a median of −40% (range, −19% to −57%; $p = 0.003$). After infusion the duration increased again to equal the control value.

In three preparations relative estimates were made of the mean amplitude of the high-voltage electrocortical activity signal in control, infusion, and postinfusion conditions. Tracings were made from the original recordings of electrocortical activity signals that had been rectified and processed by a leaky integrator (time constant, 1 second). Episodes of high-voltage electrocortical activity were readily identifiable as sections of integrated electrocorticogram tracings elevated above the low-voltage baseline. The raw electrocorticogram signal was also displayed and allowed confirmation of high-voltage episodes. The duration of each such episode was measured and the tracing cut out and weighed to find its area (signal power integrated over

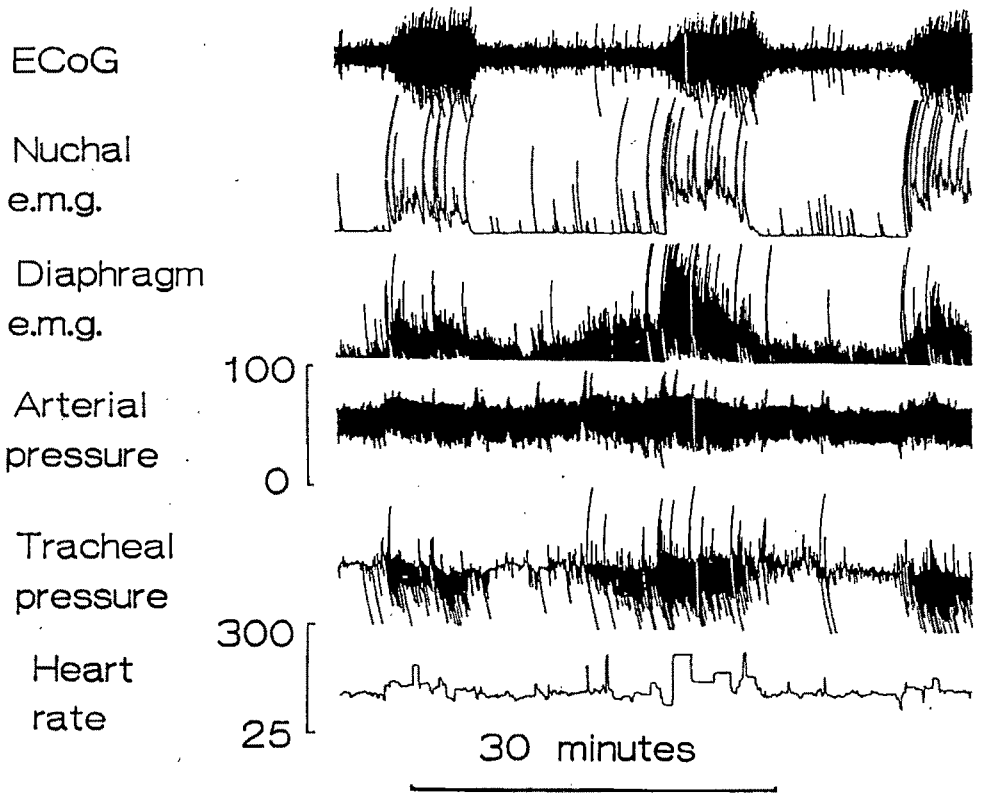


Fig. 4. Breathing, nuchal, and diaphragm electromyographic activity in a fetal lamb during recovery from clonidine infusion via intraventricular catheter. During this period hyperpnea frequently occurred, with breathing continuing in both low-voltage and high-voltage electrocortical activity as in this example.

time). The mean height was then calculated to provide a measure of the mean signal power during the episode. There were no consistent differences between control, infusion, and postinfusion values for mean heights in these preparations.

Nuchal activity. The nature of the chart recordings and of the pattern of nuchal muscle activity did not lend themselves to quantitative analysis by the methods available and no measurements were made. It was apparent that there was less nuchal activity during clonidine infusion: peaks of integrated electromyographic activity were lower and less frequent than in control conditions, although some activity was still present. Although nuchal activity remained episodic, the relation between episodes of breathing and high-voltage electrocortical activity was abnormal. During control periods nuchal activity was almost entirely confined to high-voltage as usual, but during clonidine infusions the small amount of nuchal and diaphragm activity tended to occur together during low-voltage electrocortical activity (Fig. 1). Nuchal activity increased again in the postinfusion period but had no consistent relationship to breathing.

Heart rate and blood pressure. There was no significant difference between high-voltage and low-voltage electrocortical activity in either rate or pressure. Mean control heart rate was 141.7 ± 3.3 per minute in high-voltage electrocortical activity and 137.5 ± 3.7 in low-voltage electrocortical activity (not significant by paired t test). Mean control arterial pressures were 48.8 ± .09 mm Hg (high-voltage electrocortical activity) and 52.1 ± 1.1 mm Hg (low-voltage electrocortical activity) (not significant by paired t test; all values are stated as means ± SEM). Each value is derived from 134 observations on six fetal lambs. Because low-voltage and high-voltage control data were not significantly different, values were pooled for comparison with clonidine responses. Contrary to expectation, clonidine did not lower fetal arterial pressure. The mean systolic pressure was 55.9 ± 5.1 mm Hg (control) and 56.8 ± 5.1 mm Hg (infusion) (difference not significant). However, heart rate was significantly reduced by clonidine infusion. Control mean was 158.8 ± 20.5 beats/min and during infusion the rate was 134.5 ± 18.4 beats/min ($p < 0.02$ by paired t test). Each mean is derived from a total of 134 observations.

Comment

This study confirms and extends an earlier report[5] that clonidine effectively inhibits fetal breathing by a direct action on the brain stem. In this study postinfusion hyperpnea also occurred, and both the incidence and episode duration of high-voltage electrocortical activity were reduced during and after central infusion. Infusion of clonidine was associated with inhibition of nuchal muscle activity and a fall in heart rate but fetal arterial pressure and blood gases remained unchanged.

The small cerebrospinal fluid volume and long catheters made sampling of cerebrospinal fluid impractical; thus the clonidine concentration in the cerebrospinal fluid is not known. The dose rate was 9 μg/hr or approximately 3 μg/kg/hr to the fetus (0.15 μg/kg/hr to the fetomaternal unit). The women in the study by Horvath et al.[1] received up to 1800 μg per day in two doses or approximately 12 μg/kg in each dose. If a steady state is assumed, this dose was equivalent to about 1 μg/kg/hr, but the postmedication peaks would have been higher. Thus the fetal dose rates used in this study were probably close to the maximum dose used in the clinical trials reported by Horvath et al. The infusion route directly into the ventricles probably did not affect the results because in most respects the data are qualitatively similar to those obtained in the previous study with systemic injections.[5] Clonidine did not cause apnea postnatally under physiologic conditions,[6] and a related agent, xylazine, induced tachypnea in adult sheep.[9] Clonidine had no effect on minute ventilation or breathing pattern in adult cats.[10] However, clonidine reduced phrenic discharge in paralyzed, anesthetized, and ventilated cats,[11] and clonidine and noradrenaline both inhibited rhythmic respiratory neural activity in the isolated brain stem of the newborn rat.[12] The inhibition was blocked by phenoxybenzamine, a nonspecific α-adrenergic antagonist. Under these conditions the respiratory nuclei were isolated from peripheral feedback regulation as in the fetus, and this may be a necessary condition for clonidine to cause apnea. Clonidine stimulates α_2-adrenergic receptors and reduces the rate of noradrenaline turnover in the brain.[13] We suggest that tonic activity in an α_1- or β-noradrenergic pathway is necessary to maintain fetal breathing and that fetal apnea can be caused by blocking this activity. The locus coeruleus with its high concentration of α_2 receptors[14] and adrenergic outflow to much of the brain stem is a possible site of such an action.

The mechanism of the postinfusion hyperpnea is unknown. A possibly analogous rise in respiratory rate, locomotor activity, and the incidence of body shakes in rats 8 to 12 hours follows a 10-day infusion of clonidine.[15] Both effects may result from prolonged inhibition of noradrenergic neurones, perhaps leading to an accumulation of transmitter or to hypersensitivity of postsynaptic neurones to norepinephrine. Chronic clonidine treatment has been shown to desensitize postsynaptic α_2 receptors,[16] and this represents another possible mechanism for the postinfusion hyperpnea. The increased breathing incidence in the fetus during this time was associated with an increased incidence of low-voltage electrocortical activity, although this alone could not account for the hyperpnea: breathing occasionally also occurred during high-voltage electrocortical activity in the postinfusion period. Blood gas levels were not significantly different from control during this period.

Clonidine altered the normal regular cycling of fetal electrocortical activity states, both during and after the infusion. Episodes of high-voltage electrocortical activity became shorter and the incidence of high-voltage activity was reduced during infusion, followed by recovery within 8 to 10 hours of the end of infusion. These effects differ from those reported after systemic injections, which caused an immediate but transient shift to high-voltage activity. The difference may be a result of the different time course of central clonidine levels. Systemic bolus injections produce a rapid rise and fall, whereas central infusion causes a slow rise to a steady concentration. However, in both studies the previously regular electrocortical activity cycling became rapid and irregular for some hours after administration of clonidine. Effects of clonidine on sleep state have been described in other species: it reduces the incidence of rapid eye movement sleep in rat pups,[17] and induces cortical synchronization (high-voltage electrocortical activity) in rabbits.[18] Clonidine inhibits the release of 5-hydroxytryptamine (serotonin) from raphe neurones indirectly[2] and could affect sleep-state regulation by this means. Because fetal activity is affected by sleep state, it is possible that changes in sleep-state cycling could affect motor development.

In conclusion, we have demonstrated a prolonged inhibition of fetal breathing during central clonidine infusion with prolonged postinfusion hyperpnea. Changes in electrocortical cycling also occurred. These findings support the hypothesis of a central noradrenergic drive important in maintaining fetal but not neonatal breathing, and this may be an important insight into perinatal changes in the respiratory control system. Such changes are as yet poorly understood[19] but it seems likely that failure to coordinate them could lead to respiratory instability and a tendency to apnea in the newborn. The depression of fetal breathing by clonidine may also have direct clinical significance. It has been shown repeatedly that any interference with breathing in fetal lambs results in lung hypoplasia[20] and

this is probably also true for humans.[21] Until further information is available, clonidine should be used with caution during pregnancy.

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Appendix

Preparation of artificial cerebrospinal fluid

Sodium chloride 7.12 gm
Calcium chloride 0.11 gm
Sodium bicarbonate 1.85 gm
Potassium phosphate 0.41 gm
Urea 0.24 gm

Combine to make 1L with deionized water and adjust pH to neutral by bubbling carbon dioxide through solution. Sterilize by filtration.

Dose response of thyrotropin-releasing hormone on pulmonary maturation in corticosteroid-treated preterm rabbits

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The dose-response effect of thyrotropin-releasing hormone in enhancing pulmonary maturation was investigated with six dosing regimens. Pregnant does received thyrotropin-releasing hormone (5, 10, or 50 μg/kg every 12 hours for four doses or one dose of 20 μg/kg) in conjunction with betamethasone beginning on day 25 of gestation, with betamethasone alone or saline solution used as comparison treatment groups. Half of the newborn rabbits received supplemental surfactant therapy after delivery on day 27, and all were ventilated on a ventilator plethysmography system for 30 minutes. There were no differences among the four thyrotropin-releasing hormone doses in surfactant pool sizes, compliances, or proteins leak into or out of the air spaces. The groups that received multiple doses of thyrotropin-releasing hormone had significantly higher perinatal loss rates than the single-dose group. The lungs of the group treated with thyrotropin-releasing hormone plus steroid and the rabbits treated only with steroid were more compliant than the controls without surfactant therapy, and showed significant improvements in protein leak. The addition of thyrotropin-releasing hormone to betamethasone improved several of the protein leak measurements compared with use of betamethasone alone. These results question the necessity of multiple doses of thyrotropin-releasing hormone to induce pulmonary maturation, especially when the higher perinatal mortality and the theoretical long-term effects of fetal hyperthyroidism on thyroid axis function are considered. (Am J Obstet Gynecol 1990;163:669-76.)

Key words: Thyrotropin-releasing hormone, corticosteroids, pulmonary maturation

The concept of hormonal induction of pulmonary maturation has been experimentally demonstrated and clinically applied with the use of antenatal corticosteroids for the prevention of respiratory distress syndrome in the preterm neonate.[1] However, many preterm deliveries occur too quickly to benefit from maternal corticosteroid treatments, or the use of corticosteroids is relatively contraindicated. In addition, only about 50% of preterm infants appropriately treated benefit from maternal corticosteroid therapy.[1] Several other agents have been evaluated for properties similar or additive to those of corticosteroids.[2] Thyroid hormones, alone and in conjunction with steroids, have been shown to improve many of the in vitro measurements used to assess pulmonary maturation.[1,2] Because these hormones do not cross the placenta in appreciable amounts, thyrotropin-releasing hormone, a tripeptide that readily crosses the placenta, has been investigated as a means to stimulate the fetal thyroid axis and hence increase circulating levels of thyroid hormones in the fetus. Previous rabbit and early clinical studies have used doses of 15 to 40 μg of thyrotropin-releasing hormone per kilogram of maternal body weight per day for 48 to 72 hours before delivery.[3-5] Multiple divided doses have been used to theoretically maintain elevated fetal triiodothyronine and thyroxine levels during the course of therapy. These studies have suggested improvements in pulmonary maturation with the combination of thyrotropin-releasing hormone and corticosteroids that are superior to either hormone individually. The purpose of this study was to investigate possible dose-response effects of thyrotropin-releasing hormone on induction of pulmonary maturation when used in conjunction with betamethasone, either alone or with supplemental surfactant therapy.

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Material and methods

Hormonal treatments. Time-bred New Zealand White rabbits were randomized to one of seven treatment regimens beginning on day 25 of gestation (term = 31 days) (Table I). The previous studies investigating thyrotropin-releasing hormone in this model and in clinical trials have used multiple doses of thyrotropin-releasing hormone, most commonly 20 μg/kg every 12 hours for four doses in this model.[3-6] The four dosing regimens of thyrotropin-releasing

Table I. Treatment regimens of pregnant does

Group designation	*Drug*	*Route*	*Dose*	*Timing (hr before delivery)*
5 μg/kg	Thyrotropin-releasing hormone	IV	5 μg/kg	48, 36, 24, 12
	Betamethasone	IM	50 μg/kg	48, 24
10 μg/kg	Thyrotropin-releasing hormone	IV	10 μg/kg	48, 36, 24, 12
	Betamethasone	IM	50 μg/kg	48, 24
50 μg/kg	Thyrotropin-releasing hormone	IV	50 μg/kg	48, 36, 24, 12
	Betamethasone	IM	50 μg/kg	48, 24
20 μg/kg	Thyrotropin-releasing hormone	IV	20 μg/kg	48
	Betamethasone	IM	50 μg/kg	48, 24
Steroid	Saline solution	IV	0.2 ml	48, 36, 24, 12
	Betamethasone	IM	50 μg/kg	48, 24
Control A	Saline solution	IV	0.2 ml	48, 36, 24, 12
	Saline solution	IM	0.2 ml	48, 24
Control B	Saline solution	IV	0.2 ml	48
	Saline solution	IM	0.2 ml	48, 24

IV, Intravenous; *IM*, intramuscular.

Thyrotropin-releasing hormone purchased from Bachem (Torrance, Calif.). Betamethasone as Celestone Soluspan was a gift from Schering Corp. (Kenilworth, N.J.).

hormone we used were selected to bracket the doses used previously. In addition, we administered 20 μg/kg in a single injection to evaluate the efficacy of a single dose regimen. Rabbits in all four thyrotropin-releasing hormone dose groups also received betamethasone to evaluate a dose response to thyrotropin-releasing hormone in hormonal combination treatment. The dose of betamethasone used (50 μg/kg) was previously shown to achieve the same beneficial effects as higher doses in this model while minimizing perinatal mortality.[7] Two control groups were used to evaluate possible differences between the single and multiple intravenous injections. The guidelines for the care and use of animals approved by our institution were followed during the experiment.

Preparation of rabbits. On day 27 of gestation the pregnant does were lightly anesthetized with intravenous diazepam, given supplemental oxygen via face mask, and delivered via cesarean section with use of spinal anesthesia. The newborn rabbits were weighed and given 10 mg/kg ketamine and 0.1 mg/kg acepromazine by intraperitoneal injection. The trachea of each rabbit was isolated and a tracheal tube made from a 18-gauge needle was tied into the trachea. The chest was compressed and released as 0.2 ml of 0.45% sodium chloride containing either 1 μCi iodine 125–labeled albumin or natural sheep surfactant (50 mg total lipid per kilogram of body weight) with 1 μCi ^{125}I were injected intratracheally to alternate fetuses from each litter.[3]

After the intratracheal injection approximately five breaths of 100% oxygen were given with an anesthesia bag and manometer to initiate ventilation. The rabbits were then transferred to a ventilator plethysmography system temperature controlled at 37° C.[3] Initial ventilation was with 100% oxygen at a rate of 40 breaths/min, an inspiratory time of 0.7 seconds, a peak inspiratory pressure of 35 cm H_2O, and an end expiratory pressure of 0. The tidal volume was measured frequently with a pneumotachometer and maintained at 10 to 12 ml/kg by adjusting the individual peak inspiratory pressures.[3]

Each rabbit received 0.2 ml of saline solution containing 1 μCi ^{131}I-albumin via the external jugular vein immediately after placement on the ventilator. The rabbits were ventilated for 30 minutes and then killed with intrathecal injections of lidocaine. The chest was opened and a heparinized blood sample was drawn from the heart. An aliquot of this sample was used to measure P_{CO_2}. A second aliquot was used for measurements of labeled albumin and hemoglobin concentration. The sex of each rabbit was determined by examination of the internal gonads.[8]

Processing of samples. The lungs of the newborn rabbits were thoroughly lavaged with five aliquots (1 to 1.5 ml each) of 0.9% sodium chloride.[3] The pooled volume was recorded as the alveolar wash. The lungs were removed and weighed. The alveolar wash, lungs, and blood aliquots and triplicate samples of the ^{131}I and ^{125}I used for the initial injections were counted for radioactivity. The lungs were then homogenized in 4 ml of 0.9% saline solution and the volume recorded. The contribution of intravascular blood to the radioactivity associated with the lung was calculated by measuring the hemoglobin content and radioactivity of the blood and the lung, and was subtracted from the total radioactivity of the lung.[3]

Lipid extracts of aliquots of the alveolar wash and the lung homogenate were prepared with chloroform/methanol (2:1, vol/vol).[9] The extracts were treated with osmium tetroxide; saturated phosphatidylcholine was isolated by alumina column chro-

matography and quantified by phosphorus assay.[10, 11] The protein content of each alveolar wash was quantified.[12]

Materials. Radiolabeled albumin was prepared by iodination with carrier-free ^{131}I or ^{125}I (New England Nuclear, Boston) using chloramine-T and monomer standard bovine serum albumin (Miles Laboratories, Elkhart, Ind.). The iodinated albumin was extensively dialyzed, and the incorporation was verified by trichloroaceteic acid precipitation. The surfactant was isolated by a series of differential and sucrose density-gradient centrifugation steps from alveolar washes from adult sheep.[13]

Data analysis. Animals were excluded from the final analysis if upper airway leaks occurred during placement of the trachea tube, a pneumothorax occurred during ventilation, or the final P_{CO_2} was greater than 70 mm Hg. The ^{125}I and ^{131}I-albumin radioactivity of the alveolar wash and the lung tissue were expressed as the percent recovery of the respective quantities injected. A compliance value was calculated for each rabbit at 5, 10, 20, and 30 minutes after the initiation of ventilation by dividing the measured tidal volume by the peak inspiratory pressure and the body weight in kilograms. All values are reported as means ± SEM. Statistical analysis was performed using a one-way analysis of variance followed by the Student–Newman-Keuls correction for multiple comparisons. Initially an analysis was performed among the four thyrotropin-releasing hormone dose groups to identify any dose effects. If no differences were found among the thyrotropin-releasing hormone groups, they were combined into a single thyrotropin-releasing hormone group and compared with the steroid and control groups. The two control groups were not different and were combined for the analysis. Mortality rates were examined with χ^2 analysis with the appropriate degrees of freedom. Unpaired t tests were used to determine any sex-dependent differences within groups. No sex differences in any parameters were noted; sexes within groups were combined for subsequent analysis. Significance was accepted at levels of $p < 0.05$.

Results

Condition of animals. There were no perinatal losses (abortions or stillbirths) in the control group, and only one in the steroid alone group (Table II). In contrast, groups treated with the multiple doses of thyrotropin-releasing hormone had significantly higher perinatal mortality than the steroid-only or control groups ($p < 0.01$). The single 20 μg/kg dose group's loss rate was not significantly different from the steroid alone, the control, or the 10 μg/kg dose group but was less than the 5 and the 50 μg/kg dose groups ($p < 0.001$). There were no differences in the mortality rates between the multiple dose thyrotropin-releasing hormone groups. One of the 5 μg/kg litters, containing 10 fetuses, and two of the 50 μg/kg litters, totaling 16 fetuses, were delivered prematurely after the last dose of thyrotropin-releasing hormone. In terms of body weight there was no difference between the thyrotropin-releasing hormone groups, or between groups with or without surfactant treatment. The 5, 50, and combined thyrotropin-releasing hormone groups had significantly lower mean birth weights than the steroid and control groups when the surfactant treatment subgroups were combined ($p < 0.05$).

Ventilatory status. The ventilator strategy used was successful in maintaining mean tidal volumes in the desired range for all treatment groups (Table III). Among the individual thyrotropin-releasing hormone groups, the only significant difference in any of the ventilatory parameters was that the 10 μg/kg thyrotropin-releasing hormone group treated with surfactant required a higher mean peak inspiratory pressures than the respective 5 and 20 μg/kg groups ($p < 0.05$). No clear thyrotropin-releasing hormone dose effects or tendencies were seen within the respective surfactant treatment groups in terms of compliance. In the absence of exogenous surfactant, the control group required a higher mean peak inspiratory pressures than the combined thyrotropin-releasing hormone group ($p < 0.05$), and was less compliant than the combined thyrotropin-releasing hormone group and the group treated with steroid alone at 30 minutes ($p < 0.05$). These differences in compliance and peak inspiratory pressures disappeared when the rabbits were treated with surfactant. The rabbits that received thyrotropin-releasing hormone showed a 18% greater improvement in compliance at 30 minutes with surfactant therapy than the group treated with steroid only, although there were no significant differences in the final values.

Surfactant pool size. The amount of saturated phosphatidylcholine in the alveolar wash and the total lung (lung homogenate plus alveolar wash) were measured to assess the effects of thyrotropin-releasing hormone on surfactant pool size in the absence of supplemental surfactant (Fig. 1). The 50 and the single 20 μg/kg doses resulted in a twofold increase in alveolar wash saturated phosphatidylcholine over the 5 and 10 μg/kg doses, but these findings were not significant. Similarly, there were no differences among the four thyrotropin-releasing hormone doses in terms of total lung saturated phosphatidylcholine. Thyrotropin-releasing hormone combined with betamethasone treatment did not significantly increase surfactant pool size when compared with the control group. Although the nonsurfactant-treated combined thyrotropin-releasing hormone plus beta-

Table II. Summary of litters and fetuses studied

	Group					
	5 μg/kg		*10 μg/kg*		*50 μg/kg*	
Litters (*n*)	7		7		8	
Fetuses (*n*)	77		74		75	
Perinatal loss						
No.	41*		30†		48*	
%	53		41		64	
Airway leak	2		3		0	
Surfactant treatment	+	−	+	−	+	−
Pneumothorax	0	2	0	0	0	0
P_{CO_2} > 70 mm Hg	2	0	2	0	2	8
Animals used for analysis	14	16	18	13	12	12
Weight (gm) (mean ± SEM)	23.9 ± 0.9	22.4 ± 0.9	23.9 ± 0.8	23.7 ± 0.9	22.1 ± 0.9	22.1 ± 0.8

*$p < 0.01$, versus 20 μg/kg, steroid, and control.
†$p < 0.01$, versus steroid and control.

Table III. Ventilatory characteristics of newborn rabbits

	Group						
	5 μg/kg	*10 μg/kg*	*50 μg/kg*	*20 μg/kg*	*All TRH*	*Steroid*	*Control*
No surfactant treatment							
P_{CO_2} (mm Hg)	41.4 ± 1.9	44.5 ± 1.7	44.0 ± 2.0	42.1 ± 2.0	42.8 ± 1.0	49.6 ± 2.2*	41.9 ± 2.0
Mean TV (ml/kg)	10.8 ± 0.5	10.3 ± 0.7	10.6 ± 0.5	10.1 ± 0.5	10.4 ± 0.3	11.0 ± 0.5	10.4 ± 0.4
Mean PIP (cm H_2O)	23.5 ± 0.8	24.6 ± 1.7	22.8 ± 1.6	24.9 ± 1.1	24.0 ± 0.6†	24.1 ± 1.0	27.3 ± 0.9
30 min compliance (ml/cm $H_2O \cdot$ kg)	0.51 ± 0.04	0.44 ± 0.01	0.51 ± 0.04	0.44 ± 0.02	0.47 ± 0.02†	0.46 ± 0.02†	0.38 ± 0.01
Surfactant treatment							
P_{CO_2}	38.9 ± 3.1	38.3 ± 2.5	40.0 ± 2.9	41.6 ± 2.5	39.7 ± 1.3†	46.2 ± 3.2†	33.2 ± 1.5
Mean TV	11.2 ± 0.3	11.5 ± 0.3	11.9 ± 0.5	10.6 ± 0.5	11.3 ± 0.2	10.1 ± 0.8	11.3 ± 0.5
Mean PIP	15.1 ± 1.1‡	18.6 ± 0.9	17.5 ± 1.1	15.1 ± 1.1‡	16.8 ± 0.5	16.1 ± 1.2	17.2 ± 0.9
30 min compliance	0.84 ± 0.08	0.67 ± 0.03	0.74 ± 0.06	0.71 ± 0.02	0.73 ± 0.03	0.68 ± 0.04	0.67 ± 0.03

TV, Tidal volume; *PIP*, peak inspiratory pressure.
*$p < 0.05$, versus control, all TRH.
†$p < 0.05$, versus control.
‡$p < 0.05$, versus 10.

methasone group had alveolar wash and total lung pool sizes that were respectively 60% and 15% greater than the litters treated only with steroid, these differences were not statistically significant. In the surfactant-treated groups no differences were found between any of the thyrotropin-releasing hormone groups or between the combined thyrotropin-releasing hormone group, the steroid-only group, and the control in either alveolar wash or total lung saturated phosphatidylcholine.

Protein leak. The percent recovery of intravascular ^{131}I-albumin in the alveolar wash and total lung was used as a measurement of the accumulation of intravascular protein in the alveolus and lung tissue; a higher percent recovery indicated greater protein leak into the lung (Fig. 2). The alveolar wash recovery was similar for the four groups. Although surfactant treatment decreased the recovery of ^{131}I-albumin by more than fourfold, there were no thyrotropin-releasing hormone dose-dependent effects. The total lung recoveries similarly failed to show significant differences or a dose-related trend. The alveolar wash recovery in the combined thyrotropin-releasing hormone group was almost half that of the control in both the presence ($p < 0.05$) and absence of surfactant treatment ($p < 0.01$), and the total lung recovery was significantly decreased in the absence of surfactant treatment ($p < 0.05$). Treatment with betamethasone alone decreased the percent recovery of labeled albumin in relation to the controls in the alveolar wash ($p < 0.01$) and the total lung ($p < 0.05$) in the absence of surfactant therapy. In examining the effects of thyrotropin-releasing hor-

Group					
20 μg/kg		*Steroid*		*Control*	
6		5		5	
55		39		46	
10		1		0	
18		3		0	
2		0		2	
+	−	+	−	+	−
1	4	2	2	1	1
3	1	2	1	0	1
17	18	18	13	21	20
23.0 ± 1.1	24.1 ± 1.2	25.7 ± 0.8	25.3 ± 0.8	26.5 ± 1.4	26.2 ± 1.1

mone and corticosteroids, thyrotropin-releasing hormone plus betamethasone therapy in the combined thyrotropin-releasing hormone group significantly decreased the percent recovery of labeled albumin in relation to betamethasone alone for all measurements except the alveolar wash recovery in the nonsurfactant-treated group ($p < 0.05$).

The total amount of protein recovered in the alveolar wash showed similar responses to thyrotropin-releasing hormone therapy independent of dose. The addition of surfactant therapy decreased the alveolar wash total protein from 115.7 ± 8.4 to 95.6 ± 5.6 mg/kg in the combined thyrotropin-releasing hormone group, and from 127.0 ± 8.4 to 116.7 ± 21.9 mg/kg in the group treated with steroid only. Although the thyrotropin-releasing hormone groups exhibited a 100% to 200% greater decrease with surfactant treatment than the group treated with steroid only, there were no significant differences in the amount of protein recovered from the air spaces when compared with the steroid groups. The alveolar wash protein in the control group was 242.4 ± 18.8 mg/kg, 70% to 130% higher than the hormonally treated rabbits without surfactant treatment ($p < 0.01$). Although the recovery in the control group significantly decreased to 159.7 ± 16.5 mg/kg with surfactant therapy, it remained 40% to 60% higher than in the hormonal treatment groups ($p < 0.05$).

The percent recovery of the intratracheal instilled ^{125}I reflects the movement of protein from the air spaces; a lower percent recovery indicates more movement or leak from the lung. No differences or trends occurred with the different thyrotropin-releasing hormone doses in either the alveolar wash or total lung recovery (Table IV). Without surfactant therapy the recovery in the alveolar wash in the individual and combined thyrotropin-releasing hormone groups and the group treated with steroid only was 25% to 35% less than the controls ($p < 0.05$). There were no differences between the thyrotropin-releasing hormone and steroid-only groups in alveolar wash recovery, or among any groups in total lung recovery. Surfactant therapy resulted in a higher percent recovery in (i.e., decreased protein leak from) the air spaces and lung. No differences were noted between the controls and the hormonal treatment groups.

Comment

The initial interest in the effects of thyrotropin-releasing hormone on enhancing pulmonary maturation arose from its potential as a means for transplacental stimulation of the fetal thyroid axis. Thyrotropin-releasing hormone does cross the placenta in the rat, rabbit, primate, and in humans.[14-16] Azukizawa et al.[14] demonstrated that maternal administration of 10 μg/kg of thyrotropin-releasing hormone in the rhesus monkey resulted in a fivefold increase in fetal TSH at 1 hour and a twofold to threefold increase in triiodothyronine and thyroxine at 2 hours. In humans Moya et al.[15] noted a fourfold increase in cord blood TSH and a twofold increase in cord triiodothyronine with 400 or 600 μg of thyrotropin-releasing hormone given 2 hours before delivery.

With the historical experience of corticosteroids requiring 48 hours before beneficial effects are noted, and the theory that the mechanism of action of steroids and thyrotropin-releasing hormone involve, at least in part, the receptor-mediated induction of specific enzyme systems, the studies that have examined the effects of thyrotropin-releasing hormone in conjunction with corticosteroids have used >24-hour dosing regimens.[3-6] The doses of thyrotropin-releasing hormone chosen have been based on the results of the studies outlined above. Most of the studies have used multiple doses of thyrotropin-releasing hormone in an attempt to obtain elevated levels of triiodothyronine and thyroxine in the fetus for much of the 24 to 72 hours

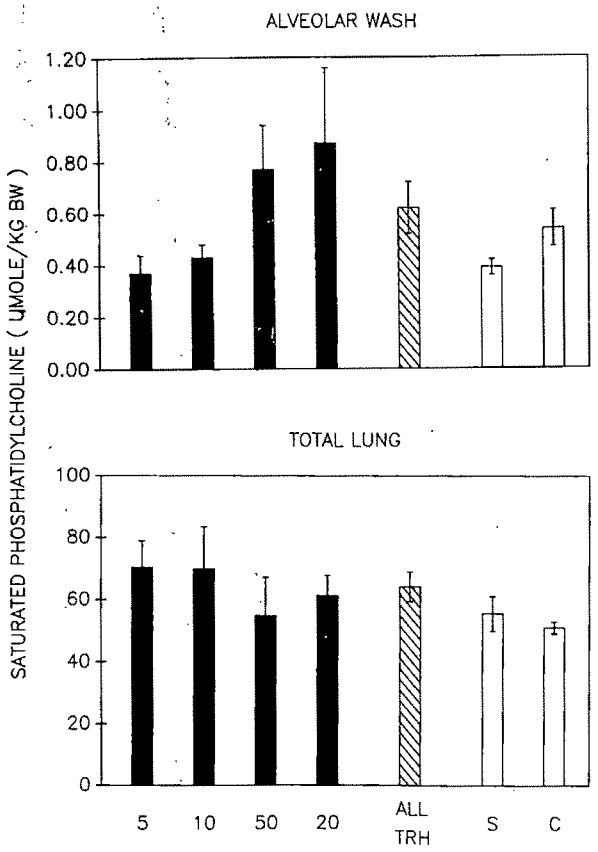


Fig. 1. Amount of saturated phosphatidylcholine in the alveolar wash and total lung (alveolar wash + lung homogenate) in the animals not treated with supplemental surfactant. There were no significant differences among the individual multiple (5, 10, 50 μg/kg) or single (20 μg/kg) thyrotropin-releasing hormone dose groups, or among the combined thyrotropin-releasing hormone *(ALL TRH)*, steroid only *(S)*, or control *(C)* groups.

of exposure. Ikegami et al.,[3] using 20 μg/kg of thyrotropin-releasing hormone every 12 hours for four doses in the 27-day preterm rabbit model, noted an improvement in compliance with thyrotropin-releasing hormone plus betamethasone relative to thyrotropin-releasing hormone or betamethasone alone when the rabbits were treated with surfactant. Suggestive improvements in these measurements and in protein leak measurements in the combination group without surfactant therapy were also noted. Oulton et al.[5] found increases in the intracellular, but not the extracellular, surfactant pool sizes in the 27-day gestation rabbit with intraperitoneal fetal cortisol injections followed by single daily doses of 40 μg/kg thyrotropin-releasing hormone beginning on day 24. No significant differences were noted among 1, 2, or 3 days of thyrotropin-releasing hormone therapy. Liggins et al.,[17] using direct fetal infusions of 25 μg thyrotropin-releasing hormone per hour over 6½ days, cortisol, or both, in the preterm lamb, found significant increases in alveolar wash–saturated phosphatidylcholine and lung distensibility and stability when compared with cortisol alone. In the one published clinical trial to date, Morales et al.[4] compared thyrotropin-releasing hormone (400 μg every 8 hours for six doses) and betamethasone (12 mg every 24 hours for two doses) with betamethasone alone. They found a significantly higher success rate (no respiratory distress syndrome if delivered within 1 week or a mature lecithin/sphingomyelin ratio if undelivered after 1 week) with thyrotropin-releasing hormone and betamethasone (61%) versus betamethasone alone (46%). In addition, the thyrotropin-releasing hormone plus steroid group required less assisted ventilation (2.1 versus 5.1 days) and had a lower incidence of bronchopulmonary dysplasia (8% versus 24%).

When our dosing regimens are compared with these studies, we have administered both higher and lower single and cumulative doses of thyrotropin-releasing hormone. The tendencies for the rabbits treated with thyrotropin-releasing hormone plus steroid to be more compliant and have larger surfactant pools than the group treated with steroid only are consistent with the findings of Ikegami et al.[3] and Oulton et al.[5] The thyrotropin-releasing hormone and steroid effects on ^{125}I-albumin recovery, suggesting increased leak from the air spaces, may represent increased surface area (increased alveolarization) or maturational effects on alveolar epithelial permeability, as noted previously with betamethasone.[7] The decreased recovery of ^{131}I from the alveolar wash and total lung indicates attenuated leak from the pulmonary vasculature into the lung and air spaces. This suggests a maturational effect of these hormones on the vascular endothelium. The combined effects of thyrotropin-releasing hormone and corticosteroids on the vascular endothelium and the alveolar epithelium are superior to corticosteroids alone. Because the proteins recovered in the alveolar wash presumably contribute to the formation of hyaline membranes and may interfere with the function of surfactant, these improvements induced by the combined hormonal treatment may play a role in the improvements Morales et al.[4] noted in terms of duration of assisted ventilation and incidence of bronchopulmonary dysplasia.[18]

This study demonstrated no differences among four different thyrotropin-releasing hormone dosing regimens. When the results are analyzed for trends that would suggest a dose response to thyrotropin-releasing hormone, no clear, consistent tendencies are found, regardless of either the individual dose size or the total amount. One alarming trend is noted. The litters treated with the multiple-dose regimens experienced a twofold to threefold increase in perinatal loss rate compared with the litters treated with a single-dose regimen. Significant mortality rates have been previously observed with thyroid hormones alone and with glucocorticoids in this model.[3, 19] Devaskar et al.[20] postulated that these hormones may deplete myocardial glycogen, which could result in fetal death. The

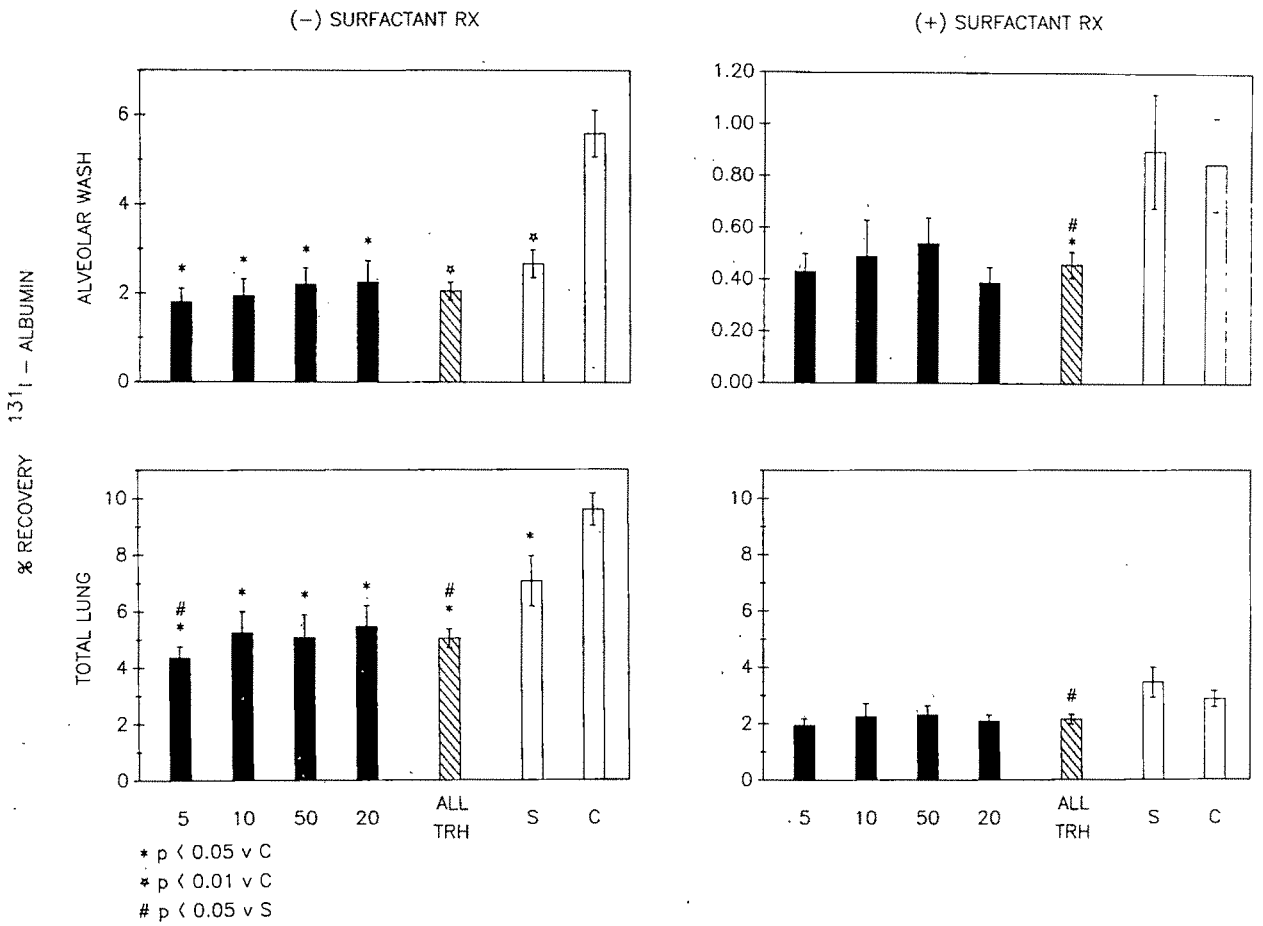


Fig. 2. Percent recovery of ^{131}I-albumin from the alveolar wash and total lung. There were no differences among the individual thyrotropin-releasing hormone dose groups, with or without surfactant therapy. The percent recovery from the alveolar wash and total lung for all the treatment groups was significantly less than the control in the absence of surfactant therapy. The total lung recovery in the combined thyrotropin-releasing hormone and the 5 μg/kg groups was also less than the steroid-only group. With surfactant treatment, only the combined thyrotropin-releasing hormone group was significantly less than the control group in alveolar wash recovery and the steroid-only group in both alveolar wash and total lung recovery.

Table IV. Percent recovery of intraalveolar ^{125}I-albumin

	No surfactant therapy		*Surfactant therapy*	
Group	*Alveolar wash*	*Total lung*	*Alveolar wash*	*Total lung*
5 μg/kg	14.8 ± 2.0	45.9 ± 2.6	36.6 ± 5.2	62.7 ± 5.1
10 μg/kg	14.1 ± 2.4	40.9 ± 5.1	32.2 ± 3.4	61.8 ± 3.6
50 μg/kg	16.8 ± 2.6	45.0 ± 4.6	40.9 ± 3.7	66.1 ± 2.7
20 μg/kg	13.6 ± 1.6	42.7 ± 3.7	36.9 ± 3.2	68.5 ± 3.4
All TRH	14.7 ± 1.0*	43.6 ± 1.9	36.3 ± 1.9	64.7 ± 1.9
Steroid	16.7 ± 1.4*	46.8 ± 3.2	36.1 ± 3.8	59.1 ± 6.2
Control	23.3 ± 2.0	50.2 ± 3.2	40.9 ± 3.3	66.7 ± 3.0

TRH, Thyrotropin-releasing hormone.
*$p < 0.05$, versus control.

higher loss rate observed with the multiple doses of thyrotropin-releasing hormone could result from more severe or complete myocardial glycogen depletion.

The lack of a dose response in our study raises questions with regard to the mechanism action of thyrotropin-releasing hormone in enhancing pulmonary maturity. The systems responsible for the observed effects of thyrotropin-releasing hormone may not respond to thyroid hormones in a dose-dependent manner, may do so at lower levels than those induced by the doses of thyrotropin-releasing hormone used here, or may be a result of other actions of thyrotropin-

releasing hormone, either directly as a neurotransmitter, or indirectly from stimulation of fetal breathing or release of other hormones, such as prolactin.[17,21] These maturational processes may be initiated once a threshold concentration of thyrotropin-releasing hormone, which possibly completely binds the appropriate receptors, is reached. The results obtained with the single 20 μg/kg dose suggest that these levels need only be maintained for a relatively brief period of time. This hypothesis questions the efficacy, and the necessity, of using multiple doses of thyrotropin-releasing hormone to stimulate a system that may be activated after the first dose.

In this light, two points must be considered that may be of more than theoretical interest. The first concerns the increased perinatal mortality observed with the multiple-dose regimens. Although use of thyrotropin-releasing hormone did not increase mortality in the clinical study, the question of increased risk with the multiple-dose regimen is raised. The second point to be considered concerns the concept of receptor plasticity and hormonal imprinting. The number and affinity of hormone receptors change during the perinatal period.[22] This adaptive process is sensitive to internal (genetic) and external (hormonal) influences. The final receptor numbers and binding capacity, and hence the adult behavior, of a particular system may be substantially affected by perinatal hormonal levels. Permanent alterations in the hypothalamopituitary-thyroid axis in rats can be induced by neonatal hyperthyroidism.[23] Whereas the in utero levels of thyroid hormone achieved by maternal administration of thyrotropin-releasing hormone are surpassed by the postnatal thyroid surge, the effect of transient fetal hyperthyroidism on adult function of the thyroid axis is unknown and may prove to be deleterious. If subsequent clinical trials confirm the utility of this combined hormonal therapy, investigation of the efficacy of a single dose of thyrotropin-releasing hormone should be undertaken to minimize the risks to which the fetus is exposed in obtaining these benefits.

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LETTERS TO THE EDITORS

Editors' note: Readers may note we are publishing more Letters to the Editors in an effort to reduce the backlog and improve the publication time.

Definition of primiparas

To the Editors: I write in reference to the letter (Gooden MD. Defining "primiparas" [Letter]. AM J OBSTET GYNECOL 1989;161:1417) and reply (Thomson M. Reply [Letter]. AM J OBSTET GYNECOL 1989;161:1417) that appeared in the November 1989 issue of the JOURNAL. I agree with Dr. Goodman that the term "primipara" should be used as it is defined obstetrically. I trust that Dr. Thomson would not refer to the patient in question as being para 1 but will call them "1 para" by using the term primipara. Those who are and hold themselves to be educated professionals are held to a higher standard than generic dictionary writers. I urge the editors of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY to avoid the misuse of the term "primipara" within the covers of the JOURNAL.

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Twin-to-twin transfusion syndrome

To the Editors: Drs. Danskin and Neilson should be congratulated for reevaluating the diagnosis of the twin-to-twin transfusion syndrome (Danskin FH, Neilson JP. Twin-to-twin transfusion syndrome: What are appropriate diagnostic criteria? AM J OBSTET GYNECOL 1989; 161:365-9). Their study focused on the posthoc situation after the delivery of a growth discordant pair (>20%) with or without hemoglobin difference of ≥5 gm/dl. They concluded correctly that neither permits a definitive diagnosis of the syndrome.

Twin-to-twin transfusion syndrome is a rare cause of intertwin growth disparity,[1] which mainly results from environmental rather than genetic factors. The findings of Danskin and Neilson are therefore unsurprising.

The twin-to-twin transfusion syndrome is an important and dangerous complication that must not be left for postpartum diagnosis. Bebbington and Wittman[2] listed the ultrasonographic criteria including (1) intertwin growth discordancy, (2) amniotic sacs of divergent size, (3) signs of hydrops in either twin or congestive heart failure in the recipient, (4) same sex of twins, (5) single placenta, and (6) separate cords differing in size and number of vessels. In addition, percutaneous umbilical cord sampling may disclose highly divergent hemoglobin levels. Finally, Doppler velocimetry has been claimed to diagnose twin-to-twin transfusion.[3]

In our experience, intensive and possibly invasive evaluations may be indicated in highly discordant twins as revealed by ultrasonography.[4] When combined with other features that indicate the twin-to-twin transfusion syndrome, rescue of one or both twins may be possible.

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Reply

To the Editors: I appreciate the interest of Dr. Blickstein in our article. I am well aware of the ultrasonographic features of florid twin-to-twin transfusion syndrome. They are not subtle and they were described in our article. However, the question that we have been addressing (and to which this article contributes) is whether the presence of vascular anastomoses in monochorionic placentas contributes to a spectrum of adverse outcome (i.e., less unmistakable manifestations of twin-to-twin transfusion syndrome). Such studies require that appropriate criteria are established for diagnosis of the condition after birth. Dr. Blickstein may not be surprised that the finding of a hemoglobin difference >5 gm/dl plus a birth weight difference >20% is not definitive proof of twin-to-twin transfusion syndrome, but I suspect others will be surprised. Varying reports of the pattern of Doppler umbilical artery flow velocity waveforms in apparent twin-to-twin transfusion syndrome undoubtedly reflect a lack of satisfactory diagnostic criteria—thus concordant waveforms,[1,2] discordant waveforms,[3] cyclically discordant waveforms,[4] and no consistent pattern[5] have all been reported. Clearly, it is vital that the type of placentation be reported in any publication on the subject of twin-to-twin transfusion syndrome, but this is frequently not the case. We have found that vascular anastomoses in monochorionic placentas do not, in the absence of rare florid twin-to-twin transfusion syndrome, exert a strong influence on fetal growth or umbilical artery flow velocity waveforms.[6]

The management of twin pregnancy is perhaps the example par excellence in obstetrics of uncontrolled

observation passing as scientific fact leading to inappropriate intervention. The long-cherished concept that routine bed rest, for example, prolongs twin pregnancy can only now be confidently laid to rest.[7-9] If Dr. Blickstein has controlled data to indicate that invasive procedures improve fetal outcome in twin-to-twin transfusion syndrome he should be less coy in sharing such important observations with the medical community.

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The importance of considering clinical usefulness in the evaluation of medical laboratory tests

To the Editors: The rapid proliferation of medical laboratory tests is providing the practicing physician with the choice of a wide variety of determinations, methods, and manufacturers. In the field of infectious diseases for example, because of the recognition of new infectious agents and the development of monoclonal and molecular techniques there is a remarkable increase in the number and types of laboratory tests and there is a wide variety of packaged test kits prepared by many different manufacturers. These tests are being marketed to both laboratories and physicians. The clinician is increasingly required to select (or have selected for him) not only a particular determination but also a specific method and manufacturer.

In the past, most laboratory methods were evaluated and chosen on the basis of the sensitivity and specificity of the method compared with a reference method. In some cases, further evaluation included the determination of the positive and negative predictive values of the test as applied to particular populations. Tests with "high marks" with these evaluations were then selected if their availability and cost were satisfactory.[1] It is apparent however, that even the best tests selected with these criteria may have little or no clinical usefulness.

Just two examples from the field of perinatal infectious diseases demonstrate the importance of clinical usefulness.

Example 1—Prediction of recurrent genital herpesvirus near the time of delivery—use of cesarean section:

For the past 15 to 20 years sensitive and specific tissue culture tests were used serially during pregnancy to identify asymptomatic genital herpes infections in high-risk women. If the tests were positive near term, the child was delivered by cesarean section. It was not until 1987 that a study was conducted to determine whether these serial prospectively conducted tests actually identified women who had herpes infections at the time of delivery.[2] The investigations showed no correlation between the serial test results and the presence of herpes infection at delivery. These tests are no longer recommended.[3,4]

Example 2—Use of immunoglobulin M (IgM) antibody to *Toxoplasma gondii* to diagnose acute infections during pregnancy:

With the availability of specific IgM tests for antibody to *Toxoplasma gondii* these tests have been used to identify pregnant women who may have had primary infection with this organism during pregnancy. If a woman had serologic evidence of primary toxoplasmosis, she was counseled on the possible serious effects on the developing fetus and the importance of starting chemotherapy or possibly a therapeutic abortion. In a more recent study, however, we showed that high titers of this antibody may persist for many years in some persons.[5] Thus we now know that the presence of high IgM titers cannot accurately distinguish a very recent or current infection from one that may have occurred several years earlier.

These two examples show the importance of considering clinical usefulness in the selection of tests to be used in the care of patients. In both instances large numbers of patients were tested at considerable cost in the belief that the tests had clinical value. In addition, major clinical decisions were made on the basis of the test results. Whereas the determinations provided relatively sensitive and specific information about the presence or absence of genital herpesvirus or IgM antibody to *Toxoplasma,* many years passed before the value of this information was considered in relation to the clinicaal problem. For herpes, after about 20 years of testing a study was finally conducted and it showed that the serial tests taken earlier in pregnancy did not predict the presence or absence of genital herpes at delivery. Thus on a scale of 0 to 100, the clinical usefulness of the test used for this purpose was very low.

Similarly for *Toxoplasma,* the tests themselves could be made quite accurate for the detection of IgM antibody; however, when we studied the persistence of this antibody we found that a number of patients retained very high antibody levels for many years. Therefore the presence of high titers of IgM antibody could not be used to accurately document the occurrence of an acute infection during pregnancy. Again, for this purpose the test had a very low clinical usefulness.

These are just two examples of medical laboratory tests with low clinical usefulness for the clinical applications described. The same tests have higher clinical usefulness when applied to other clinical problems. Many other examples could be described.

Numeric estimates of clinical usefulness can be determined by use of the same statistical methods used for sensitivity, specificity, and predictive values. However, the analysis must relate the laboratory data to the clinical information that is of greatest importance. For perinatal herpes, the most significant clinical usefulness would be the relation between the maternal preterm herpes cultures and herpes infection of the newborn child. This clinical usefulness has never been determined. The next most useful clinical usefulness is the relation between preterm cultures and genital herpes at delivery. This was finally determined in 1986 and led to the discontinuation of these procedures.

Clearly we must consider the clinical usefulness of each test in relation to the purpose for which it is being used. We must examine the clinical usefulness of the many tests that are already in use and we must require the inclusion of studies and analysis of clinical usefulness for new tests as they become available for clinical medicine.

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Surrogate parenting contracts

To the Editors: La Puma et al.'s "Clinician Opinion" article about surrogacy (La Puma J, Schiedermayer DL, Grover J. Surrogacy and Shakespeare: The Merchant's contract revisited. Am J Obstet Gynecol 1989;160: 59-62) should not pass without at least a brief rebuttal; the numerous errors of fact therein would require a more extensive response beyond the scope of the available space.

It is one thing for the authors to opine that obstetricians should not own or operate a surrogate parenting agency. It is quite another for them to tell obstetricians not to provide medical services to the parties of surrogate contracts.

To begin with, I know of no surrogate parenting agency in which a physician, much less an obstetrician, is a party to a surrogate parenting contract. Surrogate parenting contracts involve an agreement with various provisions between the surrogate and the intended parents, usually husband and (infertile) wife. Physicians are justifiably involved in providing medical care of various types to these three parties: infertility evaluation of all parties, infertility counseling, referral to surrogate parenting agencies, infectious disease screening, genetic counseling, psychiatric evaluation, artificial insemination, management of infertility in the father and surrogate, in vitro fertilization (for gestational surrogates) and ovum donation,[1] and of course prenatal care of the surrogate. As the authors correctly note elsewhere,[2] dual relationships with one's patients are ethically troublesome and should be avoided, so physicians should not contaminate their medical role with their patients by adding another one as gatekeeper, administrator, or owner of a surrogate parenting agency in which these same patients have been served.

It is presumptuous, if not ridiculous, to categorically reject surrogate parenting contracts as "unethical" per se. Surrogates, no less than living organ donors, obtain a great deal of emotional gratification in their role.[3-5] The infertile couple clearly enjoys having a biologically related child to raise, but also immeasurably appreciates the surrogate's altruism. Further, >95% of surrogacy arranagements are concluded without adverse result. Physicians' attempts to "protect" potential surrogates from themselves by rejecting, boycotting, or criminalizing surrogacy are no more justifiable than prohibiting organ donation by living donors in some transplant centers.[6]

There is unfortunately a great deal of ignorance and misinformation about surrogate parenting. La Puma et al.'s oversimplistic and biased article does not advance the cause of truth about this matter and certainly does not serve the interests of their infertile patients. Rather, obstetricians should be aware of the potential benefits, as well as risks, of collaborative reproduction for all the parties involved.

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Reply

To the Editors: Dr. Wettstein suggests that surrogate pregnancy should be a medical treatment, such as artificial insemination. We suggest that there is such widespread confusion about surrogacy that it is easy to miss our point.

Surrogacy is not a medical treatment. Obstetricians should not be forced to consider withdrawing, withholding, or offering surrogacy, as if it were. Surrogacy is a nonmedical process that may lure physicians into bad business arrangements and can make unwitting middlemen of obstetricians.

In regard to transplantation ethics, a fetus is not a kidney. A fetus has no duplicate; surrender of a fetus is different from donation of a kidney. Living related kidney donors can consent or refuse to donate; surrogate mothers currently have no such choice. Sanctioning "collaborative reproduction" restores the paternalism of old, making the obstetrician both deliverer and parent.

We appreciate Dr. Wettstein's comments, and we encourage other readers to avoid confusing surrogacy with medical treatment.

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Can shoulder dystocia be predicted?

To the Editors: I feel that James O'Leary, MD, and Helen Leonetti, MD, have done a great disservice to their colleagues who are practicing obstetricians. In their article "Shoulder dystocia: Prevention and treatment" (Am J Obstet Gynecol 1990;162:5-9), they give the distinct impression that most if not all shoulder dystocias should be anticipated and/or predicted and thus prevented by performing abdominal delivery. They present several tables identifying prepregnancy historical risk factors, antepartum risk factors, and intrapartum risk factors. Unfortunately they do not present any scientific data to show which risk factor or combination of risk factors would provide reasonable indications for a cesarean delivery. I believe that if Dr. O'Leary and Dr. Leonetti are honest with themselves and with other readers of the Journal they will agree that to prevent one shoulder dystocia dozens of unnecessary cesarean sections with their attendant morbidity and mortality would need to be performed. Unfortunately the legal profession has access to our professional journals, and I feel that articles like this can and will be used against anyone unfortunate enough as to find himself with a severe shoulder dystocia and an injured infant. It is a rare obstetric patient indeed that does not have at least one or several of the risk factors mentioned by the authors.

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Reply

To the Editors: McLeod (McLeod A. In discussion: Hopwood HG Jr. Shoulder dystocia: Fifteen years' experience in a community hospital. Am J Obstet Gynecol 1982;144:162-6) states: "that 'shoulder dystocia occurs cataclysmically' *must be* challenged; in many, if not a majority of cases, *it can and should be anticipated* [italics added]." He goes on to state: "All of these risk factors are identifiable and in most cases *should be* interpreted as a warning sign [italics added]."

Eight years later these same statements are still valid. The intent of our review article was to reemphasize the importance of risk factors for macrosomia and to outline a rational approach to dealing with the issue.

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Hyperbaric oxygen therapy for air embolism complicating operative hysteroscopy

To the Editors: Baggish and Daniell (Baggish MS, Daniell JF. Death caused by air embolism associated with neodymium:yttrium-aluminum-garnet laser surgery and artificial sapphire tips. Am J Obstet Gynecol 1989;161:877-8) reported two deaths caused by air embolism complicating operative hysteroscopy with laser surgery. Hyperbaric oxygen therapy was not mentioned in their article.

Immediate therapy with hyperbaric oxygen, however, must be remembered and should be encouraged for those patients with suspected air embolism. Hyperbaric oxygen therapy, a combination of compression-recompression and hyperoxygenation, is effective in the treatment of air embolism in patients who survive the initial insult. Hyperbaric oxygen decreases intravascular bubble size (on the basis of Boyle's law) and increases the driving pressure of oxygen into tissue, and thus reduces ischemia. The time between embolism and the time of hyperbaric oxygen treatment may determine the outcome in these patients. If necessary, air transportation should be used, either via a pressurized cabin for maintaining sea level pressure or by instructing the pilot to fly as low to the ground as safely possible.[1-3]

Gynecologists performing operative hysteroscopy, with or without laser surgery, must maintain a high index of suspicion concerning air embolism when confronted with acute respiratory failure and/or focal or general neurologic deficits in an otherwise healthy

woman. A sharpened awareness about appropriately timed hyperbaric oxygen treatment may improve outcome for some patients. Early consultation with a physician skilled in hyperbaric oxygen therapy is essential. Hyperbaric consultation can be obtained without charge 24 hours a day through the Divers Alert Network, Duke University, Durham, N.C., at (919) 684-8111.

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Reply

To the Editors: Dr. Tur-Kaspa's point is well taken. Unfortunately, the article published in the JOURNAL was a brief communication, and space limitations prevented us from reporting all the cases of catastrophic injury associated with the intrauterine use of artificial sapphire tips. One additional case of gas embolism (not cited in the article) was quickly recognized and the patient was transferred to a hospital equipped with a hyperbaric oxygen chamber. The patient survived but was left with a neurologic deficit.

In the two cases we reported in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY the events proceeded rapidly and cardiovascular collapse occurred with alarming speed. Whether hyperbaric oxygen could have saved those patients' lives is not known. Whether such facilities were readily available is still another question.

More important is the most direct remedy, i.e., to avoid this catastrophe by selecting other, safer modalities in the first place. Use of bare fibers and liquid media will preclude the risk of gaseous embolism.

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Fluid cooling of artificial sapphire tips of laser

To the Editors: Drs. Baggish and Daniell state in their article (Baggish MS, Daniell JF. Death caused by air embolism associated with neodymium:yttrium-aluminum-garnet laser surgery and artificial sapphire tips. AM J OBSTET GYNECOL 1989;161:877-8) that "... the use of sapphire tips for intrauterine laser surgery is associated with grave hazards for the patient." This is not a valid conclusion.

What they should have concluded and what laser manufacturers caution against is that gas, because of the high flow rate required, should not be used to cool the tips in the uterine cavity. There is no hazard, theoretical or demonstrated, if a fluid is used to cool the tips.

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Reply

To the Editors: In response to Dr. Loffer we offer the following:

The artificial sapphire tip may be applied safely for intrauterine surgery with two provisos: (1) Liquid cooling is utilized; (2) there is no chance for mistakenly instilling gas.

The manufacturer has the responsibility to design a fail-safe system to accept *only liquid* as the cooling mechanism. Unfortunately, coaxial fibers fitted with sapphire tips can optionally be cooled with gas. A recent article[1] published in *Contemporary Ob/Gyn* documents that gas cooling is still an alternative. Speaking at a laser seminar as recently as January 26, 1990, a recognized enthusiast of the sapphire tip contact technique presented data about laser laparoscopy and advocated cooling the sapphire probe with carbon dioxide gas at a flow rate of 400 ml/min. Although this flow rate may be interpreted as better than the 1 to 2 L/min recommendation cited above,[1] nevertheless it is unsafe when viewed in the context of a device directly in contact with tissues (blood vessels). No data whatsoever have been presented in the literature to indicate that gaseous delivery is safe under these circumstances.

In regard to intrauterine surgery the use of sapphire tips is unwarranted for ablation since this operation is better accomplished with a bare fiber. Septa and adhesions may be cut effectively with scissors or alternatively by argon or KTP 532 laser–delivered fibers. Recently bare extruded cutting fibers for use with any neodymium:yttrium-aluminum-garnet laser have been introduced. The extruded Nd:YAG fiber is very safe, concentrates Nd:YAG laser energy to a fine focal point, and best of all requires no cooling.

The Nd:YAG laser and the Nd:YAG contact laser accounted for the largest number of laser incidents, 37%, according to a recent Food and Drug Administration report.[2] This sobering testimony adds further support to our conclusions. Until absolute assurance can be provided that gas (air, nitrogen, or carbon dioxide) cannot gain entry into the artificial sapphire tip cooling mechanism, the system should be considered dangerous for intrauterine surgery and for that matter any other vascular site.

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Survival in a fetus with sacrococcygeal teratoma and hydrops

To the Editors: Langer et al. (Langer JC, Harrison MR, Schmidt KG, et al. Fetal hydrops and death from sacrococcygeal teratoma: Rationale for fetal surgery. AM J OBSTET GYNECOL 1989;160:1145-50) reported on three fetuses with sacrococcygeal teratoma and hydrops, a combination of findings with a high rate of perinatal death.[1] One of the three underwent resection of the tumor at 24 weeks and was returned to the uterus. Hydrops resolved and cardiac output decreased, based on echocardiographic and Doppler measurements. From their experience the authors recommended that fetal surgery may prove to be the most effective treatment for fetuses with sacrococcygeal teratoma and hydrops.

We recently treated two newborn infants with sacrococcygeal teratoma and hydrops without fetal surgery, and both survived. Detailed descriptions are to be published.[2] They were born at 30 and 33 weeks and thus were more mature than those in the study of Langer et al. The latter infant had severe respiratory insufficiency despite maximal ventilatory support and vasodilator infusions, and oliguric acute renal failure. Removal of the tumor on the second day of life led to an immediate improvement in respiratory function, with PaO_2 increasing from 48 mm Hg with use of 100% oxygen to 253 to 357 mm Hg intraoperatively. This allowed a decrease in the FIO_2 to 0.45 by the first postoperative day and extubation on the tenth day. Renal function returned in a pattern typical of recovery from acute tubular necrosis. The former case, delivered at 30 weeks, also had respiratory insufficiency that improved after surgery. Both infants are presently alive and without neurologic, pulmonary, or renal sequelae.

We therefore agree with the assertion of Langer et al. that cardiopulmonary physiology improves after tumor resection. However, affected infants born as early as 30 weeks can survive without intrauterine tumor removal. Allowing gestation (and thus fetal lung maturation) to continue constitutes an alternative to fetal surgery for affected fetuses closer to term (28 to 30 weeks). However, the combination of a sacrococcygeal teratoma and hydrops reflects severe physiologic instability; fetal death is an ever-present risk.[1] A delay in tumor resection to allow further lung maturation may result in stillbirth. One of the fetuses of Langer et al. died the day before planned fetal surgery; we were able to delay 3 weeks in a fetus of later gestation (21 vs 30 weeks). If fetal surgery has a role in sacrococcygeal teratoma, we suggest that it may be indicated in fetuses with hydrops detected before 28 weeks.

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Response declined

Ascertainment bias in diabetic outcome data

To the Editors: Drs. Damm and Molsted-Petersen have retrospectively studied a group of infants born to mothers with diabetes in an effort to determine a trend in the rate of congenital malformation (Damm P, Mølsted-Petersen L. Significant decrease in congenital malformation in newborn infants of an unselected population of diabetic women. AM J OBSTET GYNECOL 1989; 161:1163-7). They found that this rate has decreased, particularly over the last 5 years, and ascribe this improvement in outcome to better control of maternal diabetes. However, ascertainment bias may have seriously compromised their findings. The study group was identified through the records of infants born after 26 weeks' gestation. Therefore if a mother with diabetes was found to have a fetus with a congenital anomaly in the second trimester and elected to have a termination, this case would be missed according to the methodology described by the authors. Prenatal diagnostic procedures, particularly ultrasonography and maternal serum α-fetoprotein testing, have become more widely used over the time period under study, and the sensitivity and accuracy of ultrasound examination for congenital anomalies has improved significantly.

It appears possible that the authors have documented the enlarging role of prenatal diagnosis in the care of diabetic women and the subsequent termination of anomalous fetuses. The authors state that the "decline in congenital malformations was not due to an increased rate of induced abortions." However, no data are presented to support this statement. Indeed, a change in the overall rate of induced abortion would not necessarily be expected because improved diagnostic techniques have allowed for more selective use of termination.

The authors may certainly conclude from their study that the risk of delivering a child with a congenital defect has decreased in their sample. However, the question remains as to whether this finding results from a decreased frequency of anomalies because of better metabolic control or from improved detection because of advances in second-trimester fetal diagnosis.

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Reply

To the Editors: We welcome the opportunity to respond to the relevant comments of Drs. FitzSimmons and Davidson. The primary goal of our study was to investigate the incidence of congenital malformations in infants delivered by mothers with diabetes. We therefore decided only to consider infants born after 26 weeks' gestation. Drs. FitzSimmons and Davidson speculate that this cutoff point leads us to miss malformations diagnosed by antenatal screening and followed by termination in the second trimester. Furthermore, they hypothesize that the demonstrated decline in congenital malformations could be caused by better antenatal

screening followed by elective abortion rather than improved maternal diabetic control.

The outcome of all diabetic pregnancies (deliveries and abortions) in our hospital has been registered consecutively in the entire study period, especially with regard to malformations. As described in our article the abortion rate has been nearly constant over the years; in fact, a significant decrease in induced abortion from 12.8% to 5.6% was observed from the period 1977 through 1981 to 1982 through 1986 in White Classes D and F.

Since 1978 antenatal screening for malformations has been done in our department by ultrasound and amniotic fluid α-fetoprotein determination, and since 1982 serum α-fetoprotein determination also has been included. Only one single diabetic pregnancy since 1978 has been terminated because of a malformation diagnosed by second-trimester screening. This was a case of anencephaly diagnosed by ultrasonography and α-fetoprotein; the pregnancy was terminated in the seventeenth week of gestation. The mother was in White Class F with diabetic nephropathy and proliferative retinopathy; preconceptionally she had been strongly advised against pregnancy. This one case will obviously not change the message of the study, namely, that a significant decrease in congenital malformations in newborn infants of mothers with insulin-dependent diabetes has occurred in the period 1982 to 1986 in comparison with the previous 5-year periods. The cause for this decrease in congenital malformation is as previously argued in our article and is probably multifactorial. Our data indicate that the decline in congenital malformations only to a minor degree is caused by improved antenatal screening. We therefore still believe that the decline in congenital malformations is mainly the result of the following two factors: a high frequency of planned pregnancy, which is essential in women with diabetes to reduce the frequency of congenital malformations in the outcome of pregnancy and overall improved diabetes care and metabolic control in young women with diabetes in Denmark during the 1980s.

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Rapid determination of fetal sex

To the Editors: I would like to comment on the article by Pinckert et al. (Pinckert TL, Lebo RV, Golbus MS. Rapid determination of fetal sex by deoxyribonucleic acid amplification of Y chromosome–specific sequences. Am J Obstet Gynecol 1989;161:693-8). I disagree with the conclusion that this technique-technology "appears to be a reliable method to rapidly determine fetal sex that also can be used diagnostically to identify translocated Y-chromosomal material."

With three false-positive "male" results in 35 fetal sex determinations and approximately a 10% error rate, this is hardly accurate enough for "screening." Quite clearly the problems arise in relying solely on deoxyribonucleic acid study results and not deoxyribonucleic acid in conjunction with "some other sex determination technique."

It has been documented that visualization of the fetal external genitalia in early pregnancy by Fetal Anatomic Sex Assignment (Fetal Anatomic Sex Assignment is a Service Mark of John D. Stephens, MD, and is registered in U.S. Patent and Trademark Office, July 1990) is essentially 100% accurate and even has the capability of "correcting" laboratory errors.[1]

It has also been subsequently shown (and I believe that the case of the 15p+ de novo Y translocation has previously been "published"[2]). In this case ultrasound revealed female external genitalia followed by amniocytes, which showed 46,XX,15p+. Q and C banding indicates that this abnormal 15 chromosome is possibly a t(Y;15). Both parents were shown to have normal karyotypes. A repeat ultrasonogram at 20 weeks again showed female external genitalia. This implied de novo Y;15 translocation with only Yq, mainly heterochromatic area involvement. The couple elected to continue the pregnancy. After delivery skin biopsy showed a positive deoxyribonucleic acid Y-chromosome–specific probe in an otherwise "normal" female infant. This was also repeated and confirmed at The University of Gainesville in Florida (personal communication).

The other two cases (cases 1 and 3) merit discussion because in those cases "reliance" on the deoxyribonucleic acid Y probe as a screening test would have been incorrect in case 3 and probably would have correctly diagnosed male sex but would have missed the 45,X cell line. In case 3 the patient was 41 years old at the time of amniocentesis, which revealed female external genitalia. The amniocytes showed 46,XY. The infant was subsequently born and was confirmed to have testicular feminization syndrome. In case 1 ultrasonography revealed male external genitalia and the amniocytes showed 45,XO/46,XY; although all such information of normal male external genitalia was given during counseling, the couple terminated the pregnancy. The mosaic karyotype was confirmed in fetal skin.

The most recent "experience" with confirmation of ultrasonography, chromosomes, and deoxyribonucleic acid Y probe (performed at The University of California Medical Center, San Francisco) was a case of 45,X/46,X dicentric Y chromosome; the fetus had female external genitalia on the ultrasonogram and a positive deoxyribonucleic acid Y probe. The couple elected to terminate the pregnancy. Pathologic study confirmed female external genitalia, and mosaic karyotype was also subsequently reconfirmed.

Therefore I disagree with the conclusions made by Pinckert et al.: "These characteristics make polymerase chain reaction sex testing an ideal tool for prenatal studies."

The only value of this technology would be in cases in which the chromosome studies have already been performed and there is sex chromosome mosaicism; the value lies in investigating and identifying translocated Y-chromosomal material. The major usefulness in such cases would be for discussion regarding the recommendation that gonads be removed in phenotypic females with Y-chromosomal material.

Visualization of the fetal external genitalia in early pregnancy, which can be achieved at 12 weeks for males and 14 weeks for females, is more reliable and is the more "ideal" tool for prenatal studies, particularly as a noninvasive tool for genetic counseling when there is a family history of X-linked conditions and when the couple wishes to avoid invasive techniques.

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Reply

To the Editors: Dr. Stephens' letter contains a few points that require a response. First, the three false-positive results were obtained with the dot blot method and not the polymerase chain reaction method; that was the point of the article. Second, the Y;15 translocation reported in our article is not Dr. Stephens' case, although we have studied such a case for him. Third, the two paragraphs regarding his reported abstract are not pertinent; if he wishes to have his work reviewed, he should submit it for peer review. Fourth, the recent case described by Dr. Stephens does serve to remind the reader that the test is designed to determine the presence or absence of a deoxyribonucleic acid fragment and not the genital sex. The fetal genital sex was determined by ultrasonography and we assume Dr. Stephens approves of this. Finally, the remaining sections of the letter are advertisements for Dr. Stephens' patented ultrasonographic determinations of fetal sex and do not require a response.

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Use of the T-ACE questions to detect risk-drinking

To the Editors: Sokol et al. (Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. Am J Obstet Gynecol 1989;160: 863-70) studied a technique to identify pregnant "risk-drinkers" for whom targeting unique interventions might be appropriate. However, we do not think their instrument succeeds as a screening tool.

Two issues are relevant to screening for maternal alcohol use. The first is whether any alcohol consumption during pregnancy is acceptable. The threshold for adverse outcomes from maternal alcohol consumption is not known. A linear rather than threshold model of toxicity best explains behavior abnormalities caused by prenatal alcohol exposure.[1] The entire maternal intake range before pregnancy was correlated with both Apgar score and rate of spontaneous abortion.[2] Although some adverse outcomes may require high prenatal exposures, lower levels also may have detrimental consequences. The authors used a history of ≥1 ounce of absolute alcohol per day as their threshold for risk drinking. The T-ACE questions may be insensitive to lower, but clinically important, levels of drinking.

A second issue is underreporting of alcohol consumption during pregnancy.[3] The methods used by the authors to quantify alcohol consumption are susceptible to this bias. The item in the T-ACE instrument that had the strongest association with alcohol consumption was the question about tolerance. Patients who reported tolerance may be those who discount the importance of alcohol use. They may be a group more likely to report their intake accurately and are less prone to the underreporting bias. Thus the T-ACE instrument may be less sensitive than this study suggested for detecting those women who underreport risk-drinking.

A score of 2 or more on the T-ACE questions suggested a high level of alcohol consumption. A lower score should not be interpreted as an indication that counseling and follow-up about alcohol use are not indicated. Rather than a "Papanicolaou smear," as the authors suggest, the questions are more analogous to an electrocardiogram. A "normal" test does not exclude significant problems.

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Reply

To the Editor: The utility of our T-ACE questions as a simple screening device to identify women who drink enough alcohol to potentially damage their unborn offspring is questioned in the above letter on two bases.

First, it is speculated that the T-ACE questions may be insensitive to low, but clinically important, levels of drinking. However, screening for "any use" with T-ACE is not the issue. Rather, we recommend asking all patients whether they ever drink any alcoholic beverages. Heavy drinkers rarely have a level of denial leading to a negative answer to this question and occasional-to-moderate drinkers uniformly answer positively. The T-ACE questions are then asked of all drinkers, and drinking patterns are explored fully in those who are T-ACE positive. Finally, we recommend abstinence during pregnancy to all women who do drink, although we interpret the literature to indicate no detectable clin-

ically important impact from an occasional drink. Even with this strategy, it can be anticipated that many embryos, possibly the majority (perhaps 70% of American reproductive-age women are not abstinent), have some alcohol exposure because many pregnancies are unplanned. In the real world of patient care, we most surely would not want to recommend pregnancy interruption to a woman who presents for a pregnancy test and indicates that she had a few drinks before pregnancy recognition.

The usefulness of T-ACE as a screening test does not rest on whether there is a threshold. Rather, it is based on a well-documented dose-response phenomenon—more alcohol exposure, greater damage.[1] The goal is to identify the heavy drinker. This is the most cost-effective approach to the goal of preventing alcohol-related birth defects. The problem, of course, is that very few women who drink heavily are currently identified by obstetrician-gynecologists. We believe that T-ACE can help identify them.

The second objection is that underreporting may have biased the results of our study. Underreporting surely occurs; indeed, it was our research group that documented and defined the extent of this problem during pregnancy. The only significant determinant of an increase in underreporting was found to be evidence of problem drinking (high Michigan Alcoholism Screening Test [MAST] score), probably mediated by psychologic denial.[2, 3] In the study under discussion, T-ACE positivity was associated with MAST positivity; thus reported tolerance would not be associated with overreporting, as speculated in the letter. T-ACE *will* miss some at-risk pregnancies, at least the 30% we reported, but it can be expected to detect a substantial fraction of the heavier drinkers, most of whom are now unidentified. If, indeed, the prevalence of heavy drinkers were higher, the positive predictive value and false-positive rate of T-ACE would be improved. The sensitivity and specificity would not be affected. A lower cutoff point would result in a clinically unacceptable false-positive rate.

We agree that a negative T-ACE result does not rule out "significant problems." However, it does make them much less likely. The real question is whether T-ACE can detect not only at-risk pregnancies, but also affected offspring. We are now studying that crucial question. Preliminary results indicate that T-ACE negativity is in fact associated with a significant decrement in sonographically detectable anomalies, compared with the rate in T-ACE–positive pregnancies.

We believe that our results clearly indicate that screening with T-ACE is clinically useful.

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Cervical cancer: Role for progesterone during pregnancy and contraception?

To the Editors: Epidemologists agree that etiologic factors in cervical cancer are complex and multiple. Factors mentioned most recently in connection with this tumor include cigarette smoking and oral contraception, which paradoxically are almost nonexistent in rural areas of developing countries where the tumor is most common. Sexual behavior is traditionally accepted to underlie all theories of cervical neoplasia with early age of onset of coitus or multiple sexual partners thought to be most significant. The role of reproductive factors on the other hand has remained equivocal, often relegated to a position of surrogacy to sexuality.[1] This view has persisted despite several excellent studies from developing countries that show multiparity to be an important independent risk factor.[2, 3] Further support of this view has recently emerged from new epidemiologic studies in both developed and developing countries that show a strong linkage between multiparity and cervical neoplasia.[4, 5] It is now thought that a major factor in this linkage may be progesterone rather than trauma or infection per se. This hormone is known to be immunosuppressive.

Strengthening the case for progesterone are recent studies in molecular biology that have found an interaction between progesterone and human papillomavirus (HPV). It is reported that HPV 16 encodes a protein mapped in the region of E 6 and E 7 open reading frames that will cooperate with activated ras oncogene to transform primary cells.[6] The long control region of HPV 16 is also reported to contain a deoxyribonucleic acid sequence that mediates response to both progesterone and glucocorticoids thus increasing E 6 and E 7 transcription.[7] In pregnancy progesterone enhances HPV gene expression, giving rise to increased viral copy number and increased multiplication of virus-transformed cells.[8]

Increased prevalence of HPV in pregnancy has been confirmed[9] and there are also several reports that claim faster progression of cervical cancer in pregnancy.[10] Although studies of the effect of depot medroxyprogesterone acetate on cervical neoplasia give inconclusive results, there is the question of the critical levels of progesterone required to stimulate change and whether such concentrations are obtainable through currently available progesterone contraceptives.

The possibility of primary prevention of cervical cancer through family planning is an attractive one and would be ideal for developing countries, many of which are involved in extensive family planning programs. Combination of secondary cancer preventive activities

with family planning services would also be ideal. However, an important question is whether some of the family planning devices may themselves negate the desired effect by promoting neoplastic change. It is realized that progesterone-containing contraceptives are the most widely used agents in developing countries and newer progesterone-containing vaginal and cervical devises are currently being introduced.[11] The effect of increased local concentration of progesterone because of such devises on viral transcription in the cervix should be a decent scientific concern. Recent reports that HPV 16 and 18 are highly prevalent in rural women[12, 13] add further relevance to this concern.

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Breast diagnostics in clinical gynecology

To the Editors: The article by Dr. Gleicher (Gleicher N. Breast disease programs in obstetrics and gynecology: A plea for training in mammography. Am J Obstet Gynecol 1989;161:267-70) addresses what I hope will be one of the most significant directions for training gynecology specialists in the near future. Combining primary gynecology and quality breast diagnostics will dramatically increase the compliance of American women with current mammography recommendations. I have evidenced this increased compliance in my practice with the combination as described in this article.

As a practicing gynecologist, I have completed Dr. Tabar's levels I, II, and III advanced courses in breast diagnostics. In addition, I will be spending 2 weeks in Sweden studying with Dr. Tabar in a unique one-on-one training experience. As a result of my training, I have incorporated breast diagnostics into my practice; I am finding small occult cancers that previously I was missing on physical examination alone. My patients have the benefits of being evaluated by mammography and, when indicated, dedicated breast ultrasonography, fine-needle aspiration biopsy, and needle localization for use with surgical biopsy. These combinations of services often eliminate the need for further diagnostic workup. Providing these services to my patients only enhances the already established primary care relationship between myself and my patients. Patients like being able to have their annual examinations and their mammograms done in one location and under the direction of one central primary care physician. The result is a more responsible and comprehensive continuity of care for these women. Patients leave the office knowing the results of their mammograms, and they are educated and advised about any further diagnostic workup that might be necessary.

Because of our access to large numbers of women, I believe that to effectively change the death rate from breast cancer we as gynecologists must ultimately accept the responsibility for women's breast care. I clearly understand the obstacles that face gynecologists in undertaking this endeavor. Establishing an acceptance within the medical community of quality mammography interpretation by the gynecologist would be a major step forward in current breast care standards. To establish this acceptance, the American College of Obstetricians and Gynecologists must aggressively pursue expert training for its physicians before specialty certification, and then be committed to educating the rest of the medical community on the value and importance of this new approach. I have witnessed these benefits in my own practice, and I am confident that as a gynecologist, I have and will continue to effectively increase compliance to life-saving mammography.

Richard W. Cross, MD

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Reply

To the Editors: I am pleased to find a concerning experience from a fellow gynecologist. I would also like to reiterate Dr. Cross' point that the quality of mammography reading must be the basis for everything.

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The complex nature of egg transport through the oviduct

To the Editors: I read with special interest the article by Pulkkinen and Jaakkola (Pulkkinen MO, Jaakkola U-M. Low serum progesterone levels and tubal dysfunction—A possible cause of ectopic pregnancy. AM J OBSTET GYNECOL 1989;161:934-7) in which the authors demonstrated low prouterine gradients of electrical activity at the fimbrial end and weak propulsive forces in terms of electrical bursts and inactive areas in patients with low progesterone levels. They speculated that these phenomena were related to the higher incidence of ectopic pregnancies in patients with progesterone deficiency.

The definite forces of egg transport, however, may not depend on muscle contractions at all, as Halbert et al.[1] demonstrated with the complete blockage of muscle activity in an in vivo model by infusion of isoproterenol. Totally against expectations, the transport of stained cumulus egg masses was of even shorter total duration. As a consequence, the importance of the ciliary apparatus in effecting ovum progress was emphasized.

However, as shown in a woman with Kartagener's syndrome,[2] the ciliary movement also probably is not essential.

A recently advanced hypothesis includes special arterial cushions around the intramural part of the tube as an arterial, pulse-triggered pump for egg transport.[3]

In general, the propulsive mechanism seems to be of very complex nature and the occurrence of tubal implantation of the conceptus may not be explained by certain inactive areas of muscle activity leading to partially slower egg transport through the oviduct. This is further assisted by the fact that in a substantial group of tubal pregnancies (23.8%[4] to 50%[5]) the corpus luteum is found on the contralateral ovary. In one possible explanation of this fact, the ovum is released into the cul-de-sac, and pickup by the contralateral tube might be variably delayed, thus leading to implantation in a normally active tube. The other mechanism as to how an egg can enter the contralateral tube is via the uterus, and this might even depend on higher propulsive forces to reach the implantation site.

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Reply

To the Editors: We concur with Dr. Egarter when he says that the propulsive mechanism in the oviduct is complex in nature. As evidence against the role of the smooth muscle in ovum transport, Dr. Egarter cites the case where, although muscle activity was completely blocked by isoproterenol, there was nevertheless rapid ovum transport. A different complexion is put on the matter if we consider two factors: (1) Dr. Halbert and his co-workers studied only the ampulla, not the isthmus, and (2) isoproterenol is excitatory to cilia.

The smooth muscle plays a role in the transport of ovum surrogates through the ampulla.[1] The number of ciliated cells in the isthmus is small and ciliary currents may not be exclusively in the uterine direction.[2] The contractions of a thick muscle layer are apparently significant for the propulsive mechanism in this part of the oviduct, partly because the contractility of the smooth muscle changes the intraluminal pressure that moves the luminal contents.[3] Contractility is seen as electrical activity. With the same method used as that in the oviduct, it has been shown that there is a relation between luminal transport and the spread of electrical activity, also in the epididymal duct.[4]

The article by Brokelmann, about arterial cushions in the oviduct, to which Dr. Egarter also refers, contains no information about ovum transport.

On the face of it, the mechanism suggested by Dr. Egarter, i.e., that the ovum first enters the uterus through one oviduct and is then propelled to the other, seems unlikely and is not supported by experimental findings (except in vitro fertilization). The mechanisms by which ectopic pregnancy may develop include, among other things, a large passenger ovum (possibly from the contralateral ovary, as suggested by Dr. Egarter), impaired ciliary activity in the ampulla, postinfectious anatomic changes, and, especially in the isthmus, dysfunctional smooth muscle. As we have suggested, a possible parameter would be a low progesterone level. In our detailed analysis it was found that sine wave activity in the oviduct had the best correlation with serum progesterone level, and it is known that sine

wave electrical activity also correlates with nonpropulsion in the intestines.[5]

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Appropriate screening tests

To the Editors: Although I was impressed by the skill in which Dr. Chervenak and associates make an argument for the routine offering of medically unindicated ultrasonography to pregnant women (Chervenak FA, McCullough LB, Chervenak JL. Prenatal informed consent for sonogram: an indication for obstetric ultrasonography. Am J Obstet Gynecol 1989;161:857-60), there are some significant flaws in their logic that I feel must be pointed out. Without quoting actual data, the authors state "Established benefits currently outweigh harms, because the harms of false-positive and false-negative diagnosis can be minimized and the potential harms described by Kremkau may not ever be established." Although it is true that falsely abnormal results can be minimized in expert hands, there is little question that, when the routine offering of medically unindicated ultrasonograms becomes part of standard practice, most obstetric ultrasonography would be performed with insufficient expertise to obviate falsely abnormal results.

The authors further state that the most that can currently be reasonably assumed is that some theoretical harms might outweigh some of the benefits. They correctly point out that there is no way to know reliably whether all of the harms will eventually outweigh all of the benefits, and they state that they believe that it's unlikely that a randomized trial will be performed, or that if performed that conclusive results would result. This seems to be an excellent argument against any clear benefit attributable to routine ultrasonography. The assumption that obstetricians will provide appropriate counseling to their patients so that they can make a correct informed decision is not only not supported, but the information that obstetricians might use in providing that counseling is nowhere suggested. For a woman to make a correct informed consent about obtaining an unindicated ultrasonogram, it would be necessary for her to know the utility of that ultrasonogram with respect to her health and the health of her infant and the potential cost to her and her infant of a falsely abnormal or a falsely normal result.

In the current malpractice crisis a likely result of the routine offering of medically unindicated ultrasonograms would not be the provision of informal office ultrasonograms for a "fun look at the baby" but much more likely would be level 2 ultrasonograms performed by trained sonologists. Certainly, if studies are going to be done, this is how they are best done; however, the cost to the medical care system would be significant. At a time when many areas are struggling to increase access to care by extending Medicaid to women with incomes up to 185% of the federal poverty level, it seems onerous to add a medically unindicated diagnostic test.

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Reply

To the Editors: We appreciate Dr. Nagey's thoughtful comments and want to respond directly to his charge that "there are some significant flaws" in the logic of argument for prenatal informed consent for sonogram. Dr. Nagey's claim is that our argument is, in the technical language of logic, invalid. In particular, he claims that a conclusion other than the one that we draw follows from our premises about the goods and harms of routine ultrasound. Dr. Nagey thinks that the conclusion should be that there is no "clear benefit attributable to routine ultrasonography." This conclusion cannot follow from our premises. It is a well-known principle of logical reasoning that it is impossible to derive from a premise a conclusion that is its contradiction. Moreover, it contradicts one of the premises, namely, that there are already established clear-cut benefits to routine ultrasonography (e.g., the detection of unsuspected fetal anomalies at a time during which the pregnant woman may elect changes in her obstetric management.[1, 2] It is unfortunate that there is such a widespread misconception in the obstetric community about this certain, not uncertain, value of routine ultrasonography. What does follow from our premises is that there is no clear-cut balancing of the goods and harms of routine ultrasonography. This conclusion supports a woman's choice in this matter, namely, prenatal informed consent for sonogram.

In adition to criticizing the "logic" of our argument, Nagey makes other comments we wish to address. First, he is correct in his concern about "insufficient expertise" in the performance of routine ultrasonography, a concern that we already expressed in our article. Second, his suggestions for the counseling of pregnant women constitute a useful enhancement of prenatal informed consent for sonogram. Third, we agree that increased cost may be a significant factor. However, as

we point out in our article, the ethical significance of that potential increased cost must be addressed in the larger context of the formation of public policy in the democratic process. For example, it is possible that the increased expenditure for routine ultrasonography would reduce by a greater amount other medical expenses, such as neonatal costs, and thus be cost beneficial to society.

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Breast disease programs and mammography training

To the Editors: We are concerned about a conclusion in an article in the August 1989 issue of the JOURNAL (Gleicher N. Breast disease programs in obstetrics and gynecology: A plea for training in mammography. AM J OBSTET GYNECOL 1989;161:267-70). Dr. Gleicher concluded that gynecologists, to become interested in breast disease as part of their care of women, should undertake the performance and interpretation of mammograms.

We concur with the conclusion that gynecologists should become knowledgeable about the diagnosis and management of breast disease as a part of their residency and continuing medical education. In the programs of the American Cancer Society and the joint activities of the American College of Obstetricians and Gynecologists and the American College of Radiology, we have urged strongly that more attention be given to breast cancer, a disease that will strike one American woman in 10 during her lifetime.

Indeed, all our statements about breast cancer have emphasized that proper breast care begins with regular visits to a physician for physical examinations, followed at the appropriate age by periodic mammograms. It was the failure of gynecologists and other primary care physicians to uniformly use available breast cancer detection procedures that led the American Cancer Society, the National Cancer Institute, and many medical societies to embrace the concept of mammography as a screening procedure. The "walk-in" concept of screening mammography is less desirable than the standard medical approach, but it will reach many women who lack access to periodic examinations and mammography on any other basis.

The incorporation of mammograms into regular examinations of women is an end much to be desired. Making such examinations available in a timely and convenient manner has had the attention of many clinicians in several interested medical specialties. The correlation of history, physical findings, and the results of the mammogram are ideally made by the primary physician after consultation with colleagues.

However, we must suggest strongly that Gleicher's assertions that gynecologists can "pick up the art of mammography" by short courses or informal training would detract from the achievement of our shared objective and from the overall quality of care now afforded in most American cities.

Many of us who have been involved for three decades in the development and proliferation of modern mammography have overcome a series of problems. These include development of a standard technique to produce a valid image, constant attention to radiation safety, a concern with repeated examinations, and the acquisition of the visual acuity needed to detect and identify early radiologic signs of breast malignancy. After all these hurdles, it remains fair to observe that good mammography is most difficult to perform and interpret.

For more than a decade instruction in mammography has been part of the residency programs for diagnostic radiologists. A similar emphasis is incorporated in the training programs for radiographers. Beyond the formal training, some radiologists have subspecialized in mammography, just as others have concentrated on other areas. A vigorous set of continuing medical education opportunities provide upgrading for radiologists and radiographers about mammography. These programs are predicated on the basic skills acquired by radiologists in roentgen interpretation, radiation safety, and imaging technique. For Gleicher to suggest that gynecologists can detract from their own excellent and demanding residency programs to acquire a level of skill in a single (but intensely demanding) imaging procedure reflects a failure to appreciate the difficulties therein. For a radiologist to assume that his interest and skill in mammography, plus a few lectures or weekend courses, would qualify him to practice gynecology would be equally indefensible.

In recent years many of us in medicine have been part of a ground swell movement to make both clinical and screening mammography available to American women. Radiologists have been urged to provide screening programs in their hospital departments, offices, clinics, mobile services, and other sites. They have been urged, and even mandated by the pending Medicare screening coverage rules, to reduce the fee for screening to a figure well below prevailing rates for clinical mammography. They have been urged to work with gynecologists and other colleagues to establish a referral mechanism for women with positive findings on screening examinations. The American College of Obstetricians and Gynecologists has urged its members to become part of the breast care team with surgeons, pathologists, and other physicians.

We applaud Dr. Gleicher for his premise that gynecologists should learn more about breast disease and take a primary role in breast care. We renew our offer to work with The American College of Obstetricians and Gynecologists and with others to achieve that end, but we differ sharply with his conclusion that a gynecologist can and should become a proficient mammographer by brief and casual study.

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Reply

To the Editors: I am pleased to respond to the communication by Drs. Dodd and McLelland in reference to my article. At the same time, I am distressed about the obvious misrepresentation of my conclusions by these representatives of the American College of Radiology. I do not believe that my Clinical Opinion article ever suggested that gynecologists could or should "pick up the art of mammography by short courses of informal training." In fact, my own experience, also delineated in my article, was based on a rather extensive training process that involved didactic training as well as the attendance of courses which, in turn, were geared toward progressively increasing knowledge and reading capabilities. Most important, however, the entire program was based on a mandatory "double reading" process by two physicians. Since its inception this program always involved both a gynecologist and a radiologist within the framework of a multidisciplinary approach, which also included a surgeon.

Although the efforts of the radiology community over three decades in popularizing and improving mammography are applauded, it must be acknowledged that radiologists have so far been unable to make mammography the Papanicolaou smear of the breast. At present only an inadequately low percentage of women have entered mammography screening programs in accordance with recommendations by the authoritative bodies as Drs. Dodd and McLelland acknowledge in their letter. To blame this fact on gynecologists and other primary care physicians, as they do in their communication, is at best unfair and at worst uninformed. Gynecologists (and other primary care physicians as well) have succeeded in integrating other aspects of preventive care into their practices quite successfully. Papanicolaou smear screening is only one example. The same cannot be said for the mammography effort, mounted by the radiology community. In fact, it may be argued that this failure directly relates to who performs mammography. As stated in my article, patient convenience as well as cost considerations favor a "one-stop" annual checkup for each woman. What makes more sense than to offer every woman over age 40 a mammogram at the same time as she receives her annual physical, pelvic examination, and Papanicolaou smear? The breast is a reproductive organ, and gynecologists perform more breast examinations and diagnose more cases of breast cancer than any other specialty.

Laudably, Drs. Dodd and McLelland appear to fully support an integrated diagnostic approach toward women's health care. Why then do they oppose such an approach in the gynecologist's office? How many radiologists perform breast examinations at time of mammography? Gynecologists do.

However, the emphasis should not lie with *who* performs mammography. There is nothing predetermined to suggest that only radiologists can perform high-quality mammography. Similar arguments were heard from the radiology community when obstetricians and gynecologists started performing ultrasound scans. Today it is accepted by both communities that excellence can be found in both specialties. Although the amount of ultrasound training in obstetrics and gynecology residency programs still varies greatly, the same can be said about radiology training programs, especially in reference to obstetrics and gynecology ultrasound. I am sure that similar differences in extent and quality of training also exist in mammography training programs. Laszlo Tabar, arguably the most experienced mammographer in the world today, emphasizes this point repeatedly in his courses, which are largely attended by practicing radiologists but are open to interested gynecologists. In these superior exercises, Tabar also repeatedly makes the point that *nobody* is perfect in reading mammography films and strongly urges all mammography centers to double read *every* film.

I am puzzled then about alleged quality concerns, expressed by Drs. Dodd and McLelland in reference to a program like ours that has used a double-reading system since its inception, at a time when the majority of mammography programs administered by radiologists do not. Moreover, let us acknowledge a few additional facts. (1) Most mammograms in this country are *not* read by radiologists specializing in mammography. In fact, very few such specialists practice in this country (in contrast to Europe). (2) Mammography is among the least desired assignments in most radiology units. Only too often this responsibility falls on the most junior and least experienced individual and is passed on at the earliest opportunity.

I and other members of our specialty applaud the willingness of the American College of Radiology to engage in a dialogue with our community. Our own departmental interest in mammography was spurred by the recognition that we as gynecologists cannot actively engage in the management of breast disease without knowledge of mammography. We therefore maintain our belief that gynecologists who manage breast problems require mammography knowledge. Obviously, this does not automatically suggest that every gynecologist with minimal mammography knowledge should read films. We require ultrasound training in our obstetrics and gynecology residency programs but not all graduating residents read their own scans. We would like to urge our radiology colleagues to accept that some

gynecologists may choose to develop adequate expertise to read their own mammography films.

This issue should not be considered a turf battle between our two disciplines. Most gynecologists are more than horrified by their already existing medical liability situations and will not wish to expand it even further into the legally volatile diagnosis of breast cancer. At the same time, I cannot understand the apparent sensitivities expressed in the letter by Drs. Dodd and McLelland. Radiologists have no hesitation to enter practice areas of other specialties when they believe that a patient benefit can be obtained. When this recently happened in an area of gynecology,[1] our community welcomed our radiology colleagues with open arms.[2] We should expect the same.

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Vaginal birth after cesarean section: An appraisal of the reappraisal

To the Editors: Drs. Yetman and Nolan recently reported on attempted vaginal birth after cesarean section in 224 women (Yetman TJ, Nolan TE. Vaginal birth after cesarean section: a reappraisal of risk. AM J OBSTET GYNECOL 1989;161:1119-23). I am concerned that some of the conclusions reached in this study may not be supported by the data presented.

The authors concluded that "women who consider vaginal birth after cesarean section should be counseled with regard to the increased risk of perineal trauma." This recommendation was based on the finding of fewer lacerations in a group of women with no prior cesarean operations. Although it is almost inconceivable that an abdominal operation could predispose the perineum to trauma in a subsequent labor, it may be hypothesized that among women who undergo an initial cesarean section there exists a subgroup of women who are in some way predisposed to later perineal trauma. However, I believe there is a much more straightforward explanation for this study's findings. The 224 patients in the trial of labor group were studied by obtaining their inpatient records and meticulously searching for complications. In contrast, the 6957 patients in the control group were studied by scanning for comments in labor and delivery logbooks. This introduces substantial bias into the study. It is almost certain that actual review of the thousands of control patient' charts would have revealed large numbers of lacerations that were not recorded in the labor logbooks.

The authors also concluded: "Estimates of fetal weight at term should be a part of the decision-making process before vaginal birth after cesarean section is attempted." However, several recent studies have cautioned that current technology cannot accurately identify macrosomic infants before birth.[1] This is true even when the most sophisticated ultrasound techniques and computerized analysis are available.[2] But what if fetal macrosomia could be predicted accurately? The study's finding that infants weighing <3720 gm are more likely to be delivered vaginally than those weighing >3720 gm would still be clinically meaningless. Large babies are more likely to be delivered by cesarean section than small ones. It would have been surprising if this did not apply for the prior cesarean group. In light of the admittedly strict criteria used to diagnose arrest of dilatation, it is remarkable that 47% of the women with infants >3720 gm were able to avoid repeat cesarean operations. In any case the fetal weight recommendation was based on the observation of only 73 cases with fetal weight >3720 gm. A review of our data base reveals 1860 such cases, and 1238 (67%) of these women had successful vaginal births. We recently reported the outcomes of 301 trials of labor with infant birth weights >4000 gm.[3] The majority of these women were delivered vaginally.

Two perinatal deaths occurred in the study by Yetman and Nolan. It should be emphasized that neither case was related to a previous uterine scar. These cases may emphasize the risks of postterm pregnancy, but they do not pertain to vaginal birth after cesarean section. Although the authors found it "sobering" to note that these cases might have been prevented by elective cesarean section at term, the same statement could be made about every postterm fetal death in America.

Finally, it was perplexing that the authors considered a mandatory trial of labor (in the absence of medical contraindications) to be a "quick-fix" measure. If they meant to imply that current trial of labor recommendations were formulated in haste, I would like to remind them that National Institutes of Health and American College of Obstetricians and Gynecologists guidelines were based on the reassuring results of more than 40 studies published over the past 50 years.[4] It is clear that widespread acceptance of vaginal birth after cesarean section could quickly eliminate the need for a large portion of the 1 million cesarean operations performed in this country every year.

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Reply

To the Editors: My colleagues and I appreciate the comments by Dr. Flamm regarding our report and are pleased to continue a discussion of so timely an issue as the attempt at vaginal birth after cesarean section and all its ramifications. Dr. Flamm raises three issues that I will attempt to answer in turn.

First, he implies that any difference in the rates of perineal trauma between the study group and the control population are the result of a type of selection bias whereby the study population's complications were "meticulously" searched out while the controls were studied by "scanning" the labor and delivery logbooks. Obviously, to have meticulously studied all 8900 patient records would have been ideal, but this is beyond our capabilities. We are assured that this possible bias is more suspected than real because of the following observation. In none of the 137 successful vaginal births after cesarean section was there any difference between the logbook entries and the representation of perineal trauma found on record review. As in most residency training programs, the rate of significant perineal trauma is tracked and reported in monthly morbidity statistics at our institution. Because we practice at a military hospital and are thus indemnified from personal liability, there is no incentive for underreporting of perineal trauma in the logbooks.

With regard to estimates of fetal weight and their use in deciding to attempt a vaginal birth after cesarean section, again we must state that the fetal weight estimates must not be used in isolation of all other clinical factors that constitute appropriate obstetric care. We do believe that the use of ultrasonographic estimates of fetal weight can add information to the entire clinical "picture" that may be of importance to a particular woman who is trying to make an informed decision about whether to attempt a vaginal birth after cesarean section or undergo a repeat cesarean operation.

Finally, Dr. Flamm seems to misunderstand us with regard to the "quick-fix" measure referred to in our introductory paragraph. Let me state clearly that we have no problem with current recommendations for attempts at vaginal delivery for these women who *desire* such an attempt. There is a vast difference between a recommendation and a mandated solution. In the latter, the patient loses all control over the decision-making process and is left at the mercy of other forces. Unfortunately, the impetus for *mandating* vaginal birth after cesarean section attempts comes not from the medical community but from the insurance industry, motivated by economic interests. We are sure that Dr. Flamm would object to an outside interest that removed any of his patient's rights to make an informed, autonomous decision. It was this mandating of patient care that we were referring to as a "quick-fix" measure. We agree that acceptance of the vaginal birth after cesarean section would inevitably lead to a lower cesarean section rate. However, the persons who need to "accept" this route of birth are those women who have had a prior cesarean section, not their insurance companies, health maintenance organizations, or governmental agencies. If a competent woman is given all the data regarding a proposed procedure and is counseled nondirectively regarding options of near-equal risk, then she must retain the right to make whatever choice seems best for her. We can provide our patients no greater service than this.

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Maternal serum α-fetoprotein in pregnancy

To the Editors: We do not believe that the data provided by Milunsky et al. (Milunsky A, Jick SS, Bruell CL, et al. Predictive values, relative risks, and overall benefits of high and low maternal serum alpha fetoprotein screening in singleton pregnancies: New epidemiologic data. Am J Obstet Gynecol 1989;161:291-7) support their conclusion that maternal serum α-fetoprotein is "an important adjunctive tool for the identification of high-risk pregnancy and adverse neonatal outcome" when used as a general screen. Because maternal serum α-fetoprotein is of value in screening for specific outcomes of pregnancy, such as fetal neural tube defects and Down syndrome, it does not necessarily follow that maternal serum α-fetoprotein is of value as a screening tool for all adverse outcomes. Milunsky et al. have calculated the sensitivity, specificity, predictive value, and relative risk of an abnormal maternal serum α-fetoprotein value for various specific pregnancy outcomes but not as a general undirected screen. Such a calculation,[1, 2] on the basis of data provided in their Table I is presented in Table I.

The prevalence of the specified adverse outcomes in the authors' study population is 13.4%. When the maternal serum α-fetoprotein value is used as a general screen for any of the possible adverse outcomes, the sensitivity is 11.8% and the specificity 93.3%. The predictive value that abnormality is or will be present is 21.6% when the test result is abnormal (high or low) and 12.8% when the test result is normal. The overall relative risk of the specified abnormalities given an abnormal maternal serum α-fetoprotein value is 1.69 (95% confidence interval, 1.48 to 1.92).

If we remove from the calculation all those categories of adverse outcome listed by Milunsky et al. for which no significant relationship between either high or low maternal serum α-fetoprotein and adverse outcome is shown (stillbirth, polyhydramnios, maternal diabetes, maternal hypothyroidism and hyperthyroidism, and maternal illness), prevalence is reduced to 9.0%, sensitivity is increased to 14.3%, and relative risk is increased to 2.10 (1.80 to 2.45). However, if we further remove from the calculation fetal neural tube defects and chromosome abnormalities that are generally accepted as valid indications for maternal serum α-fetoprotein screening, the prevalence is reduced to 8.7%, sensitivity is reduced to 12.5%, and relative risk is reduced to 1.87 (1.56 to 2.19).

Table I. Recalculated data of Milunsky et al.

	All outcomes	*Outcomes with RR > 1.0*	*Outcomes with RR > 1.0 (excluding neural tube defects and chromosomes)*
RR and 95% CI	1.69 (1.48-1.92)	2.10 (1.80-2.45)	1.85 (1.56-2.19)
Prevalence (%)	13.4	9.0	8.7
Sensitivity (%)	11.8	14.3	12.5
Specificity (%)	93.3	93.3	93.3
PTL+ (%)	21.6	17.6	15.3
PTL− (%)	12.8	8.4	8.2

RR, Relative risk; *CI*, confidence interval; *PTL+*, positive posttest likelihood; *PTL−*, negative posttest likelihood.

We do not question the value of maternal serum α-fetoprotein screening in the prenatal diagnosis of fetal neural tube defects and chromosome abnormalities. However, we question its value as a general screening tool for prediction of "high-risk" pregnancy. With the figures calculated for those outcomes associated with increased relative risk, maternal serum α-fetoprotein screening detects only one in seven and misses six in seven of the pregnancies that progress to the adverse outcomes listed in Table I of Milunsky et al. Further, an abnormal test outcome results in false labeling of a pregnancy as "high risk" 8 times in 10.

We do not believe these figures justify the use of maternal serum α-fetoprotein screening as a general test for "high-risk" pregnancy. Use of maternal serum α-fetoprotein as a general screen for "high-risk" pregnancy could be evaluated more thoroughly in a double-blinded prospective trial of management comparing a "high-risk" protocol versus "routine" obstetric care in women with abnormal maternal serum α-fetoprotein levels.

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Reply

To the Editors: Gilchrist et al. are correct. Maternal serum α-fetoprotein screening cannot yet be used "as a general screen" for identifying high-risk pregnancy. However, elevated maternal serum α-fetoprotein values, in the absence of a detectable fetal defect, indicate a breach in the integrity of the maternal-fetal interface. Therefore our observations of increased relative risks for specific complications in a very carefully followed-up cohort of 13,846 women should alert the obstetrician to exercise anticipatory surveillance. It would seem injudicious to ignore a relative risk of 2 to 4.7 for oligohydramnios, abruptio placentae, preeclamptic toxemia, premature ruptured membranes, low birth weight, neonatal death, and other major congenital defects. In association with unexplained maternal serum α-fetoprotein elevations, others have noted a significant increased incidence of low birth weight,[1] fetal loss, neonatal death, and various nonleaking congenital defects.[2] The majority of pregnancies with elevated maternal serum α-fetoprotein levels conclude with a normal child. Nevertheless, such observations may serve as an early warning and hence maternal serum α-fetoprotein levels could also be used as an "important adjunctive tool."

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Treatment of cervical pregnancy with methotrexate

To the Editors: I read with interest the report by Palti et al. (Palti Z, Rosenn B, Goshen R, Ben-Chitrit A, Yagel S. Successful treatment of a viable cervical pregnancy with methotrexate. Am J Obstet Gynecol 1989; 161:1147-8). Although I appreciate the importance of this therapeutic modality, I would stress that a prerequisite is, of course, correct ultrasonographic diagnosis before severe hemorrhage occurs. Cervical suture, as described by Bernstein et al.[1] and referenced by the authors, still remains in the obstetrician's armamentarium as a potential conservative surgical aid to control massive hemorrhage in an acute situation usually undiagnosed before presentation (as originally described).

With reference to the figure in the article, although Fig. 1, *A*, clearly represents a transabdominal ultrasonogram, it is not clear whether Fig. 1, *B*, was obtained transabdominally or by endovaginal ultrasonography.

Coronal section (as defined in *Gray's Anatomy*[2] as vertical planes at right angles to the median-sagittal plane) of the pelvic organs is only obtainable by the endovaginal route. In fact a recent publication has suggested that the term *trans*-pelvic scan is more appropriate for the plane imaged when the sound beam is directed from side to side in the pelvis during endovaginal sonography.[3] Therefore, if Fig. 1, *B*, was performed transabdominally (as it appears to have been), it should be correctly termed a *transverse* section rather than a *coronal* section.

Inasmuch as methotrexate has rarely been applied to viable pregnancies, it would have been interesting to note the histopathologic findings of this case, which presumably reflect the effect of methotrexate on this viable pregnancy.

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Reply

To the Editors: We appreciate the letter by Dr. Sherer concerning our article. However, we disagree with him that coronal section of the uterus and cervix is obtainable only by the endovaginal route. With some experience, transabdominal coronal section of the uterus and cervix can be achieved by pressing the woman's lower abdomen by the sector probe, as clearly demonstrated in Fig. 1, *B*.

With regard to his second question, histopathologic examination revealed nonspecific missed abortion pathologic changes.

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Caution in use of new test for ectopic pregnancy

To the Editors: The article by Lindblom et al. (Lindblom B, Hahlin M, Sjöblom P. Serial human chorionic gonadotropin determinations by fluoroimmunoassay for differentiation between intrauterine and ectopic gestation. Am J Obstet Gynecol 1989;161:397-400) contributes to the difficult problem of diagnosing ectopic pregnancy when serial human chorionic gonadotropin titers are rising. However, several issues relevant to interpretation of a new diagnostic test are not addressed in the article. I believe that understanding more about the value of tests under different testing conditions might influence significantly readers' use of these three new tests.

Forty-six percent of the study population to whom the test was applied (N = 41) had ectopic pregnancies. This proportion is much higher than that seen in the typical outpatient American population followed to rule out ectopic pregnancy. If the proportion of patients with true ectopics was only 20%, for example, then the positive predictive value of the three tests (absolute slope, relative slope, and human chorionic gonadotropin score) would be 82%, 82%, and 83.7%, respectively. This is a clinically relevant decrease from the values for a 46% ectopic prevalence of 94.1%, 94.1%, and 94.7%, respectively. (Note that the values in Table II are actually sensitivity for the test applied to diagnose intrauterine pregnancy and ectopic, *not* predictive value, as stated).

Second, in contemporary American medical practice it is not possible to hospitalize for evaluation so many patients who ultimately prove not to have ectopic pregnancies (indeed almost 30% were not even pregnant). Thus the American physician will not always have the luxury of waiting 1 to 6 days with a patient in the hospital to gather information necessary to apply this test.

Finally, it seems unusual that five of the patients with ectopic pregnancies but none of the patients with intrauterine pregnancies were resampled on day + 1 and only two (versus 11 patients with intrauterine pregnancies) were resampled after day + 3. Could this represent some bias in the application of the test?

Susan T. Haas, MD

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Reply

To the Editors: We appreciate the considerations in Dr. Haas' letter that highlight important principles of test evaluation. Her comments concerns three items: prevalence of the disease, hospitalization time, and sample interval.

Concerning the prevalence of ectopic pregnancy in the study population (46%), we agree that this figure may seem high. However, it was the real proportion of ectopic pregnancy in the group to which the human chorionic gonadotropin score was applied. We believe that the following factors account for the high prevalence: (1) liberal use of endovaginal ultrasound, which accurately (and indeed rapidly and easily) recognized viable intrauterine pregnancies in a large proportion of early pregnant women; (b) the widespread knowledge in our community of risk determinants[1,2] implies that few ectopic pregnancies were "lost" for serial human chorionic gonadotropin determination because of late presentation and emergency surgery; (3) exclusion of cases with decreasing human chorionic gonadotropin levels, which are not compatible with viable pregnancy.

From the results presented, it is easy to extract the sensitivity, specificity, and positive/negative predictive values. We used the positive predictive value to compare the performance of the human chorionic gonadotropin score with the other methods applied (abso-

lute slope, relative slope). The positive predictive value (P), which is valuable for the busy clinician, is the conditional probability of "disease" (D+), that is, ectopic pregnancy, given a "positive" test, i.e., abnormal human chorionic gonadotropin score (T+). Thus P D+/T+ = 18/19 = 0.947 = 94.7%. The sensitivity clearly deals with the opposite proportion, the conditional probability of a positive test, given that the woman has the disease (P T+/D+). In this particular case, these fractions happen to be identical because there were one false-positive and one false-negative test result. Thus P T+/D+ = 18/19 = 0.947 = 94.7%. For the same reason, the specificity (P T−/D−) in this particular sample is identical to the negative predictive value (P D−/T−) = 21/22, where D− is "disease free" (intrauterine pregnancy) and T− is negative test result (normal human chorionic gonadotropin score).

With regard to the hospitalization time, we obviously misused the term "admitted." The majority of our patients were not hospitalized but were managed as outpatients.

Theoretically a difference in sampling interval between the two groups of cases could represent a bias. However, our calculations suggest that the small difference in sample interval does not significantly change the performance of the human chorionic gonadotropin score in this patient group. We currently use a sample interval of 1 to 2 days, which was also recommended in our article.

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Perception of teratogenic risk by pregnant women exposed to diagnostic radiation during pregnancy

To the Editors: We greatly enjoyed the article by Koren et al. (Koren G, Bologa M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. Am J Obstet Gynecol 1989;160:1190-4). The authors state in their conclusions that the perception of teratogenic risk is one of the factors that may lead pregnant women to consider pregnancy termination and that this perception is often determined or supported by wrong information given by health personnel.

We agree with the conclusions of Koren et al. inasmuch as we are faced with the same problem in our experience in reproductive counseling (Telefono Rosso in Rome). In particular, we noted that exposure to diagnostic radiation is an important risk factor as perceived by pregnant women.

Between June 1, 1988, and October 30, 1989, a total of 1097 requests for reproductive counseling were received. A total of 82 requests (7.5%) referred to exposure to diagnostic radiation. The time of exposure varied between the preconceptional period and 9 weeks' gestation. The total amount of radiation varied from 1 mrad to approximately 1300 mrad, a range that is not associated with a measurable risk for the fetus.[1,2]

In 50 cases (61%) the women had already consulted a physician. The physician gave a high-risk estimate in 37 cases (74%), giving a generic high-risk estimate in 20 cases, recommending prenatal diagnosis in 5 cases, and advising the women to consider pregnancy termination in 12 cases. It appears from our experience that a misperception of teratogenic risk from diagnostic radiation effectively exists, and that it may cause a state of anxiety in these women to lead them to consider pregnancy termination.

This misperception is often related to imprecise knowledge of the problem on the part of the physician. More specifically, we identified two major problems. The first relates to the difficulty of conveying the difference between the prospective preexposure approach to diagnostic radiation and the risk assessment after the exposure. Second is the imprecise and incomplete information on reproductive risk factors available in some standard textbooks and reviews.

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Reply

To the Editors: We thank Dr. Mastroiacovo and his colleagues for their important input on the misperception of teratogenic risk in cases of gestational exposure to radiation. With the use of the analogue scales reported in our original article we have recently completed analysis of risk perception in women undergoing diagnostic radiation.

Our results agree with the experience from Rome; the assigned perception of teratogenic risk was almost double that of other women exposed to nonteratogens (Bentur Y, Horlatsh N, Koren G. Unpublished observations).

This is certainly an important area in which obstetricians, general physicians, and teratogen consultation services could prevent a large number of unnecessary pregnancy terminations.

Gideon Koren, MD

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Conservative treatment of ovarian pregnancy by local prostaglandin $F_{2\alpha}$ injection

To the Editors: Conventional surgical treatment for ovarian pregnancy is associated with subsequent infertility. Egarter et al.[1] reported on the management of tubal pregnancy by intratubal injection of prostaglandin (PG) $F_{2\alpha}$ and additional synthetic PGE_2 analog. However, we are not aware of a report on the conservative approach of ovarian pregnancy by local injection of $PGF_{2\alpha}$. This is the first successful case of ovarian pregnancy treated with $PGF_{2\alpha}$ of which we are aware.

The patient was a 30-year-old infertile nulliparous woman who was first seen with spotting and left abdominal pain 6 weeks after her last menstrual period. Pregnancy test results were positive. Her uterus was empty, and a small ringlike structure near the left tubal region was noted by transvaginal ultrasonographic examination.

After obtaining informed consent, routine diagnostic laparoscopy was performed with confirmation of the diagnosis. After the ruptured left ovarian pregnancy was confirmed laparoscopically, laparotomy was performed to close the affected ovary. A part of the affected ovary was resected for the pathologic diagnosis and then the rupture was closed. Thereafter, 0.5 mg of prostaglandin $F_{2\alpha}$ was gently injected into the affected ovary. Then 10 mg of estrogen was instilled into the corpus luteum of pregnancy without complications. An additional dose of 3 × 0.5 mg PGE_2 (dinoprostone) was administered orally for 14 postoperative days. Serum β-human chorionic gonadotropin (hCG) and pregnancy-specific β_1-glycoprotein reached nonpregnant levels within 1 week of $PGF_{2\alpha}$ treatment. Fig. 1 shows the serum β-hCG and β_1-glycoprotein results. Lindblom et al.[2, 3] have shown that $PGF_{2\alpha}$ invariably causes powerful contractions as well as an antigonadotropic (i.e., luteolytic) action. Karsch et al.[4] have shown that estrogens can induce functional luteolysis in the rhesus monkey by acting directly within the ovary that contains the corpus luteum.

These results suggest that $PGF_{2\alpha}$ may be useful for pharmacologic treatment of selected cases of ovarian pregnancy.

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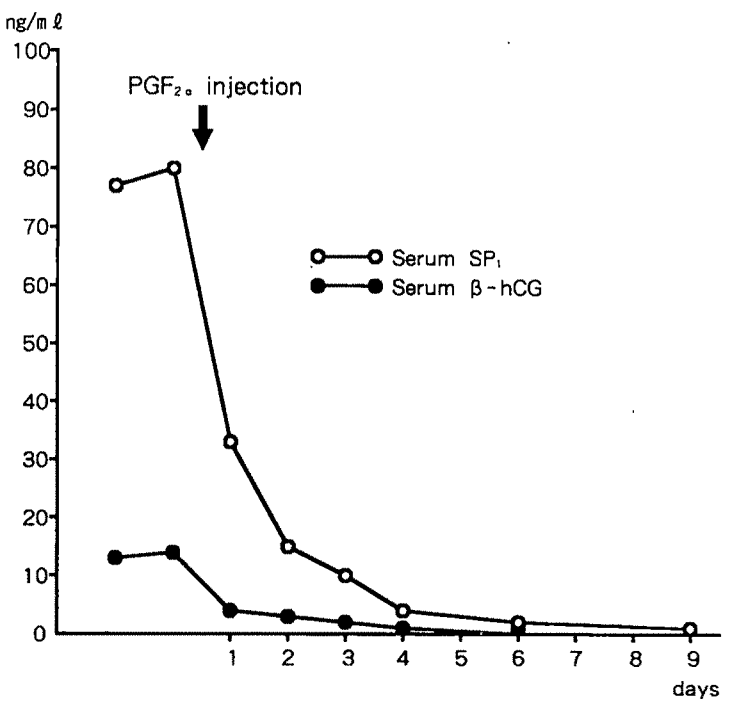


Fig. 1. Serum pregnancy-specific β_1-glycoprotein *(SP_1)* and β-hCG concentrations in this case treated with local $PGF_{2\alpha}$ injection.

Early hypothyroidism in patients with menorrhagia

To the Editors: We read with interest the article by Wilansky and Greisman (Wilansky DL, Greisman B. Early hypothyroidism in patients with menorrhagia. Am J Obstet Gynecol 1989;160:673-7) in which they showed that of 67 women presenting with menorrhagia, 15 had evidence of primary hypothyroidism. The menorrhagia disappeared on treatment with thyroxine, suggesting a cause-and-effect relationship between hypothyroidism and menorrhagia. A potential intermediary in this relationship might be the factor VIII molecule.

We recently reported a case of a 17-year-old woman who came for treatment for severe anemia caused by menorrhagia and hypothyroidism.[1] Coagulation studies showed a pattern of von Willebrand's disease (type I). There was no family history of von Willebrand's disease. On correction of thyroid status with oral L-thyroxine, coagulation defects returned to normal and menorrhagia ceased.

The association of acquired von Willebrand's disease and hypothyroidism has been recognized recently.[2-4] In some cases, menorrhagia has been reported at the time of presentation and has resolved with thyroxine therapy.

The results of coagulation studies were not reported by Wilansky and Greisman; it would be interesting to know if consideration was given to the possibility of an underlying bleeding disorder in their patients.

We believe there is a true association between hypothyroidism and acquired von Willebrand's disease, and it is the latter hemostatic abnormality that results in menorrhagia. Wilansky and Greisman are to be congratulated in alerting gynecologists to this "medical cause" of menorrhagia that can easily and effectively be treated. We would ask that in addition to thyroid function tests, coagulation studies be performed in women presenting with menorrhagia and hypothyroidism.

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Reply

To the Editors: The observation by Blesing and Hambley indicating a von Willebrand–like syndrome in certain hypothyroid patients was of great interest. We have not done detailed coagulation studies in our patients, and the frequency and significance of their preliminary observations will be determined in further studies.

The precise physiopathologic mechanism of menorrhagia in hypothyroidism has not to date been clearly established. The endocrine disturbance in pituitary-ovarian interrelationships suffices to account for menorrhagia. The observations of Blesing and Hambley point to an additional potential predisposing mechanism.

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Should amniocenteses always accompany unexplained high maternal serum α-fetoprotein levels? Who decides: Public agency, patient, or private physician?

To the Editors: I agree with Hogge et al. (Hogge WA, Thiagarajah S, Ferguson JE, Schnatterly PT, Harbert GM. The role of ultrasonography and amniocentesis in the evaluation of pregnancies at risk for neural tube defects. Am J Obstet Gynecol 1989;161:520-4) that, when ultrasonography is done as a "targeted examination" within the framework of a "comprehensive" prenatal diagnosis center where the physician is a "consultant ultrasonologist," it is possible, in selected cases, to accurately omit genetic amniocentesis testing for evaluation of a high level of maternal serum α-fetoprotein.

However, there are several other issues that must be discussed with the patient: Abnormal sex chromosomes have been detected on chromosome analysis of the amniotic fluid in a larger prospective study (the State of California Department of Health Services maternal serum α-fetoprotein program). These patients also appear to be in an increased risk category for high-risk pregnancy problems in the third trimester, and although knowledge of the abnormal chromosomes is not essential for third-trimester high-risk pregnancy management, that perspective is not alluded to in this letter or in the discussion.

The policy of the State of California Department of Health Services maternal serum α-fetoprotein program has been challenged, but the most recent "directive" is that it will continue to be the recommended standard of care that all patients have offered to them genetic amniocentesis for evaluation of a high maternal serum α-fetoprotein level, even in the presence of a normal fetal ultrasonogram.

I would be interested to know of the pregnancy outcome regarding possible high-risk pregnancy factors in the patients from this study in whom the pregnancies continued with normal fetal sonograms.

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Editors' note: Dr. Stephens is not authorized to speak for the State of California Department of Health Services.

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Reply

To the Editors: We appreciate Dr. Stephens' interest in our article on the evaluation of pregnancies at risk for neural tube defects. First, it is necessary that we respond to his statement that it is possible to accurately omit genetic amniocentesis testing for evaluation of high maternal serum α-fetoprotein in selected cases. We strongly believe that each center must evaluate its own experience with ultrasonography and amniocentesis in the detection of neural tube defects, and present this information to the patient in a nondirective fashion. Similarly, the patient should be informed that, at the present time, the accepted practice for evaluation includes amniocentesis. Until large prospective studies are completed in a number of institutions, no change in our present diagnostic approaches should be made.

Second, we are aware of anecdotal reports of chromosome aneuploidy found at the time of amniocentesis for the evaluation of an elevated maternal serum α-fetoprotein. However, the incidence of aneuploidy in the absence of ultrasonographic abnormalities of the fetus is not known. In our series no cases of aneuploidy were found in either the group that had amniocentesis, or those who chose ultrasonography only. The other large studies similar to ours report a similar experience.[1, 2] We would be interested in the California experience with "abnormal sex chromosomes." Is the incidence higher than the general population (newborn) incidence, and is it high enough to justify the risk of amniocentesis?

Third, although the analysis of obstetric complications has not been completed in our series, there are no trends that differ significantly from those reported by Milunsky et al.[3] and Robinson et al.[4] The methods for monitoring these clearly high-risk patients have not been established, but certainly most of the published obstetric complications associated with elevated maternal serum α-fetoprotein are not the result of chromosome aneuploidy. Unless the incidence of aneuploidy can be shown to be significantly increased in this group of patients with adverse pregnancy outcome, there would be no justification to add the detection of aneuploidy to the indications for amniocentesis in this subgroup of patients. We look forward to the prospective data possible through the California maternal serum α-fetoprotein screening program to help answer these questions.

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Flow cytometric quantitation of tumor-associated antigens in solid tumors

To the Editors: We read with great interest the article by Nozawa et al. on the application of the monoclonal antibody MSN-1[Nozawa S, Sakyori M, Kunihiko O, et al. A monoclonal antibody (MSN-1) against a newly established uterine endometrial cancer cell line (SNG-11) and its application to immunohistochemistry and flow cytometry. Am J Obstet Gynecol 1989;161:1079-86]. In their article the authors described a single parameter flow cytometric assay for the quantitation of MSN-1 in normal endometrium and endometrial carcinoma. Although we agree that immunofluorescence analysis using flow cytometry in conjunction with monoclonal antibodies is very useful for quantification of tumor-associated antigens in heterogeneous cell systems such as solid tumors, in our opinion future investigators should be encouraged to use multiparameter flow cytometry for this type of measurement.

All the mechanical and/or enzymatic tissue dissociation methods currently available inevitably produce a certain amount of cellular debris and dead cells. In our experience this contributes to a highly variable nonspecific fluorescent background that is difficult to allow for using single-parameter flow cytometric techniques since there can be problems in identifying the viable cells by scatter analysis alone. Conversely, simultaneous flow cytometric analysis of cell suspensions for deoxyribonucleic acid, cell volume, and tumor-associated antigens allows much better correction for fluorescent background and makes the assay much more sensitive and reproducible.[1] By plotting deoxyribonucleic acid against the 90-degree scatter pulse width, the morphologically intact cells can be separated from cell debris and clumps, and most of the small volume inflammatory cells and some of the stroma cells can be gated out. Tumor-associated antigens expression can then be calculated in the gated regions only, which contain intact tumor cells and some stromal cells. This is one of the main advantages of flow cytometry over more conven-

tional methods such as radioimmunoassay and immunoblot techniques.[1-3]

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Reply

To the Editors: We agree with the correspondents' multiparameter approach to the flow cytometric measurement of tumor-associated antigens. However, two technical matters arose in the case of the endometrial cancers we studied. First, in preliminary measurements of deoxyribonucleic acid in these cancer cells, we found that the deoxyribonucleic acid in two thirds of the well-differentiated endometrial cancers examined, of which cancers are histologically the most common type, was diploid and that in one third was aneuploid (nearly diploid). Furthermore, the deoxyribonucleic acid indices of the aneuploidy cases were below 1.2, suggesting that the strict gating of the cancer cells is very difficult.

Second, we found that the reactivity of the glycolipid antigen on the cell surface with MSN-1 antibody often changes following the fixation procedure that is a necessary step for deoxyribonucleic acid staining. Therefore in our study we performed immunostaining on nonfixed cells; this, however, makes the differential diagnosis between cell debris without nuclei and cells with nuclei difficult because the deoxyribonucleic acid of the nonfixed cells is barely stained by propidium iodide.

For these reasons it is not easy to establish a method for simultaneous measurement of MSN-1 antigen and deoxyribonucleic acid, but the combination assay of deoxyribonucleic acid and tumor-associated antigen currently seems to be the best way. We would like to accumulate basic data to develop a new supplemental method for the diagnosis of endometrial cancers, which are increasing in Japan and are sometimes difficult to diagnose on endometrial cytologic specimens.

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Effects of ritodrine tocolysis on cardiac isozymes and electrocardiography

To the Editors: We read the article by Drs. Hadi and Albazzaz (Hadi HA, Albazzaz SJ. Cardiac isoenzymes and electrocardiographic changes during ritodrine tocolysis. Am J Obstet Gynecol 1989;161:318-21), a study of 40 patients in preterm labor, with great interest. We are gratified to see confirmation of our publication of 112 patients similarly treated.[1]

In our study, serial electrocardiography and electrolyte measurements were performed before intravenous ritodrine therapy and at 6 and 24 hours of treatment. Ninety-six percent of our patients developed sinus tachycardia. ST segment depression (>1 mm) was seen in 70%, T-wave flattening or inversion in 55%, and prolongation of the QT interval in 35%. We saw no correlation between chest pain and electrocardiogram (ECG) changes. There was no direct correlation between potassium concentration and ECG changes in our study, although all treated patients showed some degree of hypokalemia relative to their pretherapy levels. Drs. Hadi and Albazzaz looked at maternal blood pressures, pulse rate, and serum electrolyte levels, but there was no attempt to correlate electrolyte changes, blood pressure changes, or pulse changes with the corresponding electrocardiographic changes.

In the current study it is unclear how frequently ECGs were ordered and whether the results of the study reflect ECGs performed at 6 hours or at 12 hours after the initiation of intravenous ritodrine therapy. Did the authors consider the ECG changes seen at the two individual time intervals? As our article clearly noted, the majority (89%) of ECG and electrolyte changes reverted to near baseline levels at 24 hours although intravenous ritodrine tocolysis was continued. These findings refute the authors' postulation that continued therapy in these patients will lead to myocyte damage. It should be noted that no change in isozyme concentration was noted during tocolysis in their study. Similarly, three previous studies have evaluated correlations of serum enzymes and/or serum creatine kinase, MB fractions, or serum myoglobin levels with ECG changes but no deviation of isozymes was seen, again arguing strongly against myocyte damage.[2-4]

We applaud the authors' conclusion that no evidence of direct cardiotoxic effects of ritodrine could be demonstrated but find their final recommendation (discontinuation of ritodrine in the face of symptoms of ischemia or ECG changes) unsettling. Our conclusion was and still is exactly the opposite. We found no correlation between chest pain and ECG changes and, indeed, like the authors, suspect that the ECG changes as seen are related to either the hypokalemia seen with β-adrenergic receptor agonists or the induced tachycardia that may cause ECG changes like those seen in athletes under similar tachycardiac conditions. In twin gestations the baseline cardiovascular changes (increased cardiac output and sinus tachycardia) are accentuated over those of singleton gestations, and the additional cardiovascular changes caused by β-

adrenergic receptor agonists would likely be more marked, as seen by the authors. Development of a sinus tachycardia is often accompanied by a relative decrease in blood flow to the subendocardium, which may cause subtle changes in maternal electrocardiograms even in the absence of functional ischemia and isoenzyme changes. This is considered a physiologic adaptation and has not been associated with proven pathologic conditions.[2] Because there is no sign of myocyte damage (normal isozymes and creatine kinase MB fractions) in treated patients, it seems unlikely that myocardial damage is occurring.[2] Our previous findings would also indicate that these ECG changes are very frequent in patients undergoing tocolysis with β-adrenergic receptor agonists and that, as previously noted, they resolve spontaneously over time even in the presence of continued intravenous tocolysis.

Finally, further insight regarding myocardial ischemia will likely require the development of an animal model to assess intracardiac ECGs during tocolysis with concomitant evaluation of cellular cardiac isozymes, gases, and lactic acid levels. In the absence of these data, there is no clinical evidence that pathologic changes in cardiac function are taking place during ritodrine tocolysis, and we suggest that ECG changes are not an indication for discontinuation of β-adrenergic tocolytic therapy.

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Reply

To the Editors: We would like to thank Drs. Hendricks and Katz for their interest in our article and for sharing some aspects of their work with us regarding this complex subject.

Our study was designed to use a combination of creatine kinase (CPK-MB), lactate dehydrogenase (LDH) subunits, LDH_1/LDH_2 ratio, and electrocardiography to investigate the possible myocardial ischemic effects of ritodrine tocolysis. It has been previously reported that the use of electrocardiography alone for diagnosis of myocardial infarct is somewhat insensitive; therefore study of cardiac enzymes, as well as ratio of LDH_1 to LDH_2, has become a significant test in these situations.[1] It has also been noted that sensitivity of electrocardiography for detection of myocardial ischemia during exercise testing is relatively low.[2]

During ritodrine tocolysis, changes such as hypokalemia (a shift of potassium from extracellular to intracellular space without total body potassium loss), low diastolic blood pressure, and maternal tachycardia are known side effects of the drug, which has been studied extensively in humans, as well as in animal models.[3, 4] Therefore we did not correlate such changes with electrocardiogram (ECG) results in our study. The fact that Drs. Hendricks and Katz did not find direct correlation between serum potassium concentration and ECG changes is not surprising.

Our study consisted of three periods: before ritodrine infusion, at 6 and 12 hours during infusion, and within 24 hours of oral drug therapy. Changes in ECGs in our study reflected those observed during ritodrine infusion periods when hemodynamic alterations were at maximum.

We found the authors' statement that the majority (89%) of ECG changes in their series reverted to near baseline at 24 hours, even though intravenous ritodrine tocolysis was continued, inconsistent with their previous report. Katz et al.[5] reported cardiovascular complications in 116 patients treated with terbutaline (a β-adrenergic receptor agonist similar to ritodrine) for preterm labor. In eight patients pulmonary edema developed, the majority with ECG changes indicative of myocardial ischemia that did not disappear for 24 hours after discontinuation of tocolytic treatment. Furthermore, the same observation was noted in one of their patients who did not have pulmonary edema. Because maternal tachycardia is a well-known effect of ritodrine therapy, the ECG changes in the authors' recent study may have been the reflection of a faster heart rate and not ischemia or, alternatively, ischemia that resolved as the heart rate decreased. This possibility was not clarified, specially when no other cardiac evaluations including enzyme studies were carried out.

Drs. Hendricks and Katz stated that ECG changes during ritodrine tocolysis are considered similar to the physiologic adaptation seen in athletes under tachycardiac conditions.They also suggest that, in the face of symptoms of ischemia or ECG changes, ritodrine tocolysis should not be discontinued. We disagree with their contentions and consider such recommendations dangerous for practitioners in the absence of adequate data. Mechanisms of cardiovascular and pulmonary complications of ritodrine are unclear at the present time. Hemodynamic effects of ritodrine should not be compared to a physiologic adaptation seen during exercise because of the following:

1. Exercise has a limited period of time (i.e., minutes to a few hours), while inotropic and chronotropic effects of ritodrine generate hemodynamic changes for 24 hours of infusion. No individual could tolerate such changes for a prolonged period of exercise. Thus it is possible that prolonged cardiac effects of ritodrine disturb the subendocardial oxygen supply/demand ratio and

precipitate myocardial ischemia and, if not treated properly, may proceed to myocyte damage.
2. Pharmacologic effects of ritodrine are different from changes considered as physiologic adaptations of exercise. These changes consist of metabolic effects, including those of glucose, sodium, potassium, renin, angiotensin, and arginine vasopressin, water homeostasis, and renal and cardiopulmonary effects. These changes individually or cumulatively predispose the patient to cardiopulmonary complications that are quite different from tachycardia seen during exercise.
3. Additional increases in blood volume and cardiac output in pregnant women, especially in twin gestations will be added risk factors to cardiopulmonary complications. The authors' most recent study, which already included two life-threatening cases of angina with normal ECGs and in one of which pulmonary edema developed, supports the notion that an ECG alone cannot be used as the sole marker of therapy in these cases.

In view of the life-threatening cardiovascular and pulmonary nature of ritodrine complications and the lack of adequate data in this regard, we believe, in the presence of ECG changes and/or chest pain, that ritodrine tocolysis should be discontinued. Furthermore, patients should be given oxygen and additional cardiac assessment and cardiology consultation should be carried out.

Finally, we agree with Drs. Henricks and Katz that further insight regarding this complex issue requires development of an animal model and more detailed cardiac studies before we suggest that ECG changes are not an indication for discontinuation of ritodrine therapy.

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Inhibitory cofactor of antiphospholipid antibody in normal pregnancy sera

To the Editors: Lockwood et al. recently reported a study to establish the causative nature of antiphospholipid antibody on adverse pregnancy outcomes (Lockwood CJ, Romero R, Feiberg RF, Clyne LP, Coster B, Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. AM J OBSTET GYNECOL 1989; 161:369-73). We would like to complement their observations with our recent finding of high levels of antiphospholipid antibody, commonly present in sera from normal healthy individuals.[1] These antiphospholipid antibodies in sera from normal healthy individuals are normally undetectable by a sensitive enzyme-linked immunosorbent assay (ELISA), but their presence is revealed when sera are first preheated at 56° C for 30 minutes before ELISA testing.[2] The antiphospholipid antibodies in normal healthy individuals were mostly IgG and exhibited the classical selective binding, as reported for antiphospholipid antibody in clinical sera, to negatively charged phospholipids including cardiolipin, phosphatidylserine, and phosphatidic acid.[1, 3] This strongly indicates the existence of heat-labile serum inhibitory cofactor(s) of antiphospholipid antibody, with such complexes in normal healthy individuals being undetectable by ELISA. The ELISA detection of such autoantibodies may thus reflect a reduction of antiphospholipid antibody–masking factor(s). In other words, any pathogenicity of antiphospholipid antibody may not necessarily result from a hyperimmune response to cell membrane phospholipids but rather a consequence of a pathophysiologic decrease in the antiphospholipid antibody inhibitor. In this regard, we have similarly found antiphospholipid antibody in 29 of 31 normal pregnancy sera after heat inactivation of the sera. We are progressing with investigations to characterize the antiphospholipid antibody regulatory cofactor and to better understand the immunogenesis of antiphospholipid antibody in nonclinical sera.

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Response declined

The local anesthetic dose is an important issue in evaluation of effects of epidural analgesia in nulliparous women

To the Editors: My colleagues and I appreciated the article by Thorp et al. (Thorp JA, Parisi VA, Boylan PC, Johnston DA. The effect of continuous epidural analgesia on cesarean section for dystocia in nulliparous women. AM J OBSTET GYNECOL 1989;161:670-5). We thought the authors did an excellent job in describing the relationship between epidural analgesia during la-

bor and incidence of cesarean section for dystocia, which may stem from such a technique. The results were analyzed, taking into account objective sources of error, and suggested a need for further investigation.

However, there was a point in the study that may need clarification. Thorp and colleagues did not specify the dose of bupivacaine administered. Indeed, the first injection was described as an "initial bolus injection of bupivacaine 0.25%," whereas the following dose was indicated as a "continuous infusion of 6 to 12 ml/hr of 0.125% solution." The mean infusion time was not given. It has been widely discussed that pregnancy increases the effectiveness of local anesthetics.[1] Therefore it has been suggested that the administered dose should be as small as possible to avoid untoward effects such as instrumental delivery and distressing motor blockade.[2] In the aforementioned work it was quite difficult to quantitate either the first or the total dose of bupivacaine. We believe this is a very important issue to address because dystocia could be related to the total amount of local anesthetic received by the patient.

In addition, we would like to reflect on the continuous infusion method used to maintain analgesia. Different epidural analgesia techniques may produce different drug levels and relative effects on the body. In a previous study Griffiths and colleagues[3] demonstrated that epidural analgesia, given by a constant infusion of bupivacaine 0.25% to 0.125%, yields a cumulative dose twice as large as that produced by repeated 0.5% bupivacaine injections. Also, in the first condition bupivacaine plasma levels were close to the toxic threshold, whereas no bupivacaine was found in plasma in the second one. In Thorp et al.'s study there was no comparison of incidence of cesarean section for dystocia between a nulliparous group of women in which a continuous infusion of 0.125% bupivacaine was given, and one receiving small 0.25% bipuvacaine top-up injections under patient request. What if the infusion time were such to allow bupivacaine accumulation? If that were the case, the results may represent an uncontrolled bupivacaine dose-effect.

Finally, the epidural use of other drugs should be explored. Opioids such as fentanyl citrate have been successfully used to relieve pain in the first stage of labor.[4] Although opioids may not be sufficient to provide adequate analgesia in all stages of labor, the synergism between local anesthetics and opioids is suitable for further investigation.[5] It may be possible that such a pharmacologic association reduces both local anesthetic dose and unwanted effects on delivery.

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Reply

To the Editors: We appreciate the interest in our research. Puppa and colleagues make several valid criticisms about any retrospective study design (i.e., there are numerous variables that were not controlled). The mean epidural infusion time was not analyzed. We agree that the total dose of bupivacaine may well be an important determinant of labor outcome. Despite the data of Griffiths et al.,[1] there are legitimate concerns about repeated boluses of 0.5% bupivacaine during labor. Continuous infusion technique is generally considered safer than repeated boluses because of the potential for toxic reactions from inadvertent intravascular bolus injection. In addition, the 0.5% bupivacaine solution would have a greater potential to affect the course of labor because it causes a more dense motor blockade than that of the 0.125% or 0.25% solution.

In institutions in which the staff are acutely aware of the potential of epidural analgesia to interfere with labor, the adverse effects may be limited. However, in institutions in which there is a lack of experience or concern, epidural analgesia may have a profound effect on the incidence of instrumental delivery and cesarean section. There is a large variation in epidural technique between institutions. Many factors involved with the epidural technique may influence the course of labor (e.g., fluid bolus, cervical dilatation at which the epidural infusion is placed, concentration of anesthetic agent, volume of anesthetic agent, and management of the epidural infusion in the second stage of labor). Perhaps as important as the epidural technique itself is the variation in the obstetrician's response to dystocia. A recent study[2] showed that with the same anesthetic service, epidural analgesia was associated with a 16-fold greater incidence of cesarean section for dystocia in the private service as compared with the clinic service. In this study,[2] epidural analgesia was associated with an increase in cesarean section for dystocia on the private service but not on the clinic service. The authors[2] speculate that the difference may be attributed to a more aggressive use of oxytocin in the clinic patients compared with the private patients. As Neuhoff et al.[2] point out, if uterine activity is not restored in a timely fashion, "the psychology of prolonged and non-progressive labor dominates management strategies, as the physicians, patients, and families become exhausted and frustrated . . .."

The question of whether epidural analgesia increases the incidence of instrumental vaginal delivery or ce-

sarean section has not been adequately addressed in a randomized prospective study. To address the selection bias issues, the ideal study must randomize patients in early labor to an epidural or a nonepidural group. In view of our article in the JOURNAL and another study[3] that shows a significant association between epidural analgesia and cesarean section for dystocia in nulliparous labors, this definitive study must be done.

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Colposcopy in diethylstilbestrol-exposed offspring

To the Editors: I would like to comment on the article by Helmerhorst et al. (Helmerhorst TJM, Wijnen HJA, Kenemans P, et al. Colposcopic findings and intraepithelial neoplasia in diethylstilbestrol-exposed offspring. AM J OBSTET GYNECOL 1989;161:1191-4) in the JOURNAL. The authors stated that, in their opinion, colposcopic evaluation of diethylstilbestrol-exposed offspring requires special expertise and is therefore recommended to be performed only in regional centers by expert colposcopists to prevent unnecessary biopsies. However, they discussed at some length the possible increased risk of intraepithelial neoplasia of the cervix and vagina in diethylstilbestrol-exposed offspring. I do not feel that their conclusions can be drawn from the information presented. I agree that expertise in colposcopy is necessary for anyone using this method to help in the identification of low-grade intraepithelial neoplasms, but I do not think that the technique of colposcopy is so difficult that individuals who practice in areas outside of regional referral centers cannot be trusted to perform the procedure. I would also seriously question these "experts" on their ability to differentiate which diethylstilbestrol-exposed patients with abnormal colposcopic findings require a biopsy and which do not.

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Reply

To the Editors: We agree with Dr. Gimbel that colposcopy is currently practiced in most gynecology departments. However, colposcopic evaluation of diethylstilbestrol-exposed women may be confusing because the physician is frequently presented with findings that in unexposed women are usually associated with cervical intraepithelial neoplasia. In our article the prevalence of abnormal cytologic findings was 9%, and in only half of these patients was a histologically confirmed low-grade cervical intraepithelial neoplasia and vaginal intraepithelial neoplasia diagnosed. These observations suggest a perilous role of colposcopic evaluation and biopsies in inexperienced hands, and we cited three previous reports with similar views.[1-3]

In the literature diverse reasons can be found to explain the different interpretation of colposcopic findings in DES-exposed individuals and in nonexposed patients. Stafl and Mattingly[2] considered the process of "arrested" immature metaplasia in DES-exposed women. Conversely, Orr et al.[1] stated that the confusing colposcopic appearances may be caused by "active metaplasia" in the extensive transformation zone, mimicking patterns of cervical intraepithelial neoplasia.

In the Netherlands, we recommend colposcopic evaluation of DES-exposed offspring in regional centers to obtain and maintain expertise. Because distances in the United States are not comparable with those in this country, we can imagine another option.

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Trend of cervical cancer in Jewish women

To the Editors: We read carefully the article by Glezerman et al. (Glezerman M, Piura B, Insler V. Cervical cancer in Jewish women. AM J OBSTET GYNECOL 1989; 161:1186-90).

The Results section contains no data with regard to a change of incidence over time nor are there any data with regard to the population base. The statement in the Comment section and final paragraph with regard to a rising trend of cervical cancer in Jewish women is therefore not justified, especially since the supposed trend has been found not to be statistically significant by the authors themselves. The statement on the ethnic distribution also is not based on presented data. It is not clear whether the population referred to in the article consists of the hospital population or the population in the Negev area. Prevalence trends in one hospital do not necessarily reflect incidence trends in the general population. It is therefore important to mention that according to the Israel Cancer Registry, which is known for its high accuracy, the incidence and

the yearly number of new cases of cervical cancer in Israel (approximately 80 new cases per year) did not change during the years referred to in this article.[1]

Today, when the cost of medical care is an important national problem and there are second thoughts about the benefit of routine screening programs for cervical cancer,[2] it seems to us that the authors' recommendation for changing national policy for cervical cancer screening in a low-risk group such as the Israeli Jewish women is not based on sound epidemiologic data and statistical analysis.

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2. McCormick JS. Cervical smears: a questionable practice? Lancet 1989;2:207-9.

Reply

To the Editors: One of the aims of our article was to point to a rising trend of incidence rates for cervical cancer in Jewish women in South Israel. This trend was expected on the basis of an earlier report that was cited in our article and demonstrated high incidence rates of preinvasive lesions of the uterine cervix among young Jewish women in Israel.[1] We stated that this trend had not reached statistical significance when compared with the population increase. Today, we have 140 Jewish women with invasive cervical cancer in our tumor registry, which covers complete data for the South of Israel. These patients were entered during a period of 30 years. Of these, 30.7% of cases were diagnosed during the past 5 years. In our Gynecological Tumor Registry, the percentage of living patients with invasive cervical cancer today equals those living with ovarian cancer (28% for each malignancy). We have been alerted by these facts.

As for other comments made by Drs. Ben Baruch and Menczer, they may want to again read our article. In the Material and methods section we have presented data concerning our population base and in Table II we have presented data on the ethnic distribution of our population. Moreover, we have elaborated on the unique position of our hospital being the only major health care center for South Israel. Virtually all patients from this defined geographic area are treated at our hospital, a well-known fact within the Israeli medical community. It is true therefore that prevalence trends and incidence rates at our hospital indeed reflect the population base that we serve. Drs. Ben Baruch and Menczer base their comments on one personal communication and on one article questioning the benefit of routine screening for cervical cancer. We feel that their conclusion is unjustified. The value of screening procedures for cervical cancer is well established, and Drs. Ben Baruch and Menczer may want to consult the literature in this regard. In the population of the South of Israel, which is served by our hospital, only one out of every five cases of cervical cancer is diagnosed in a preinvasive state. Given this situation, we feel that screening procedures are urgently needed at least with regard to the South of Israel.

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REFERENCE

1. Schachter A, Avraham E. Changing trends of cervical neoplasia in Israeli Jews. Lancet 1984;2:1150.

Laboratory identification of the lupus anticoagulant in normal pregnancy and pregnancy-induced hypertension

To the Editors: It was interesting to read the article written by Lockwood et al. (Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B, Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. Am J Obstet Gynecol 1989;161:369-73) because the results could be useful to clarify the complex relationship between lupus anticoagulant and adverse pregnancy outcomes.[1]

However, we are in disagreement concerning the detection of lupus anticoagulant in this article because it was assessed exclusively by activated partial thromboplastin time (aPTT) and mixing studies.

Lupus anticoagulant exhibits considerable laboratory heterogeneity and discordance exists to define the most sensitive and specific test for its identification.[2, 3] The aPTT is the most common assay used to screen for lupus anticoagulant, but its sensitivity varies depending on the test system used.[4] In addition, the aPTT could be normal in pregnant women with lupus anticoagulant because of the elevated factor VIII levels seen in pregnancy.[1] For this reason other screening tests are particulary useful in pregnant women.

In January 1989 we initiated in our laboratory a 2-year prospective study to establish the prevalence of lupus anticoagulant in women with hypertensive disorders of pregnancy or idiopathic intrauterine growth retardation.

Over the first-year period, we studied 20 patients and lupus anticoagulant was detected in five (preliminary results). Two of the five patients with lupus anticoagulant–positive results had normal aPTTs but abnormal kaolin clotting times,[5] abnormal dilute Russell viper venom time corrected by addition of freeze-thawed platelets,[3, 6] and the apparent increase of factor VIII and IX activities as the patients' plasma was assayed at progressively greater dilutions.[7]

On the other hand, Lockwood et al. found a discrepancy between the presence of anticardiolipin antibodies detected by an enzyme-linked immunosorbent assay and the presence of lupus anticoagulant detected by aPTT (2.2% vs 0.27%, respectively). In contrast, in a retrospective study of obstetric history in 21 women with systemic lupus erythematosus we found an equal

relative frequency (47%) of anticardiolipin antibodies and lupus anticoagulant, with an enzyme-linked immunosorbent assay method and a complete panel for lupus anticoagulant (unpublished data).

For these reasons we believe that, to establish the prevalence and biologic significance of lupus anticoagulant in pregnant women, it is mandatory to perform the lupus anticoagulant detection with tests other than the aPTT, such as kaolin clotting time and dilute Russell viper venom time.

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Reply

To the Editors: We would like to thank Dr. Riveros and associates for their interest in our study. They assert that the activated partial thromboplastin time (aPTT) "is the most common assay used to screen for lupus anticoagulant, but its sensitivity varies depending on the test system used." Indeed we chose the aPTT with the use of platelet-poor plasma precisely because it is the most commonly used "screening" test for lupus anticoagulant. Prior work has attested to its reliability in this capacity.[1] The use of more sensitive but elaborate functional coagulation assays such as the dilute Russell viper venom time and the kaolin clotting time was deemed inappropriate for a screening study.

Riveros and associates report a 25% prevalence of lupus anticoagulant, presumably utilizing the dilute Russell viper venom time and/or kaolin clotting time, in 20 patients with hypertensive disorders of pregnancy or idiopathic intrauterine growth retardation. This figure appears extraordinarily high, thus suggesting a significant number of false-positive results. In addition, their observation that patients ($n = 21$) with systemic lupus erythematosus had an equal prevalence of lupus anticoagulant and anticardiolipin antibodies (47%) is inconsistent with previous reports. Petri et al.[2] evaluated 60 patients with systemic lupus erythematosus and described a 6.7% prevalence of lupus anticoagulant as ascertained by a Russell viper venom time but a 25% prevalence of anticardiolipin antibodies. Harris et al.[3] evaluated 65 patients with systemic lupus erythematosus and related autoimmune disorders and detected a 49% prevalence of lupus anticoagulant and a 61% prevalence of anticardiolipin antibodies.[3] Thus, while Riveros and colleagues may increase sensitivity with the use of the dilute Russell viper venom time and/or kaolin clotting time, they may also increase the rate of false-positive results.

In short, Riveros and associates are quite correct to assert that the dilute Russell viper venom time and kaolin clotting time are more sensitive indices of the presence of circulating lupus anticoagulant. However, the application of these tests for large-scale screening, while useful, may be impractical.

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Role of hormones in cervical ripening

To the Editors: I would like to refer to a very interesting letter in the Correspondence section (Thiery M, DeBoever J, Merchiers E, Martens G. Hormones and cervical ripening [Letter]. AM J OBSTET GYNECOL 1989;160:1251-3).

I had previously read with great interest the article

Table I. Characteristics of the patients

Number	53
Maternal age (yr)	22.2 ± 3.1
Gestational age (wk)	39.1 ± 1.7
Gravidity	1
Parity	0
Birth weight (gm)	3187.7 ± 450.6
Time between first and second blood samples (hr)	10 ± 2

Table II. Estradiol, estriol, progesterone, and DHEAS levels in the ripe and unripe cervix ($N = 53$)

	Estradiol (pg/ml)	*Estriol (ng/ml)*	*Progesterone (ng/ml)*	*DHEAS (μg/dl)*
Unripe cervix	5563.0 ± 1014.0	193.7 ± 104.5	76.3 ± 19.7	143.3 ± 86.7
Ripe cervix	5580.9 ± 1225.4	195.1 ± 111.2	72.1 ± 19.7	234.8 ± 147.3
$p < 0.05$	NS	NS	NS	S

NS, Nonsignificant; *S*, significant.

Table III. Estradiol, estriol, progesterone, and DHEAS levels in the unripe cervix with male and female child

	Estradiol (pg/ml)	*Estriol (ng/ml)*	*Progesterone (ng/ml)*	*DHEAS (μg/dl)*
Unripe cervix, male child ($n = 28$)	5641.5 ± 904.9	175.2 ± 102.2	73.9 ± 16.6	150.9 ± 62
Unripe cervix, female child ($n = 25$)	5475.1 ± 1136.3	214.5 ± 105.2	79.0 ± 22.7	134.7 ± 108.7
$p < 0.05$	NS	NS	NS	NS

NS, Nonsignificant; *S*, significant.

Table IV. Estradiol, estriol, progesterone, and DHEAS levels in the ripe cervix with male and female child

	Estradiol (pg/ml)	*Estriol (ng/ml)*	*Progesterone (ng/ml)*	*DHEAS (μg/dl)*
Ripe cervix, male child ($n = 28$)	5628.7 ± 1286.8	187.1 ± 123.6	68.2 ± 18.1	238.9 ± 137.0
Ripe cervix, female child ($n = 25$)	5527.2 ± 1176.9	204.1 ± 97.2	76.5 ± 20.9	230.2 ± 160.7
$p < 0.05$	NS	NS	NS	NS

NS, Nonsignificant; *S*, significant.

Table V. Estradiol, estriol, progesterone, and DHEAS levels in the ripe and unripe cervix with male child

	Estradiol (pg/ml)	*Estriol (ng/ml)*	*Progesterone (ng/ml)*	*DHEAS (μg/dl)*
Unripe cervix, male child ($n = 28$)	5641.5 ± 904.9	175.2 ± 102.2	73.9 ± 16.6	150.9 ± 62.0
Ripe cervix, male child ($n = 28$)	5628.7 ± 1286.0	187.1 ± 123.6	68.2 ± 18.1	238.9 ± 137.0
$p < 0.05$	NS	NS	NS	NS

NS, Nonsignificant; *S*, significant.

Table VI. Estradiol, estriol, progesterone, and DHEAS levels in the ripe and unripe cervix with female child

	Estradiol (pg/ml)	*Estriol (ng/ml)*	*Progesterone (ng/ml)*	*DHEAS (μg/dl)*
Unripe cervix, female child ($n = 25$)	5475.1 ± 1136.3	214.5 ± 105.2	79.0 ± 22.7	134.7 ± 108.7
Ripe cervix, female child ($n = 25$)	5527.2 ± 1176.3	204.1 ± 97.2	76.5 ± 20.9	230.2 ± 160.7
$p < 0.05$	NS	NS	NS	NS

NS, Nonsignificant; *S*, significant.

by Dr. Zuidema (Zuidema LJ, Khan-Dawood F, Dawood MY, Work BA Jr. Hormones and cervical ripening: dehydroepiandrosterone sulfate, estradiol, estriol, and progesterone. AM J OBSTET GYNECOL 1986;155:1252-4) that had stressed the association of the significant elevation of maternal dehydroepiandrosterone sulfate (DHEAS) levels with the changes that precede the onset of labor.

Inspired by Dr. Zuidema's article I carried out an investigative study on the cervical ripening and hormones exclusively in nulliparous women. A total of 53 nulliparous women were included in our study group; all had single vertex presentation and a normal previous pregnancy period.

Maternal venous blood samples were taken just at the onset of the first stage of labor and at the end of the first stage from each woman. In all cases the cervical Bishop scores were <4 when the first blood samples were taken.[1] Plasma DHEAS levels were measured with a radioimmunoassay kit (DPC Coat-A-Count DHEA-SO_4 kit, Diagnostic Products Corp., Los Angeles).

Patient characteristics are summarized in Table I. Statistical analysis of the data indicated significant differences resulting from the maturity of the cervix in nulliparous women (Table II). When grouped in terms of the sex of the fetus the differences in the DHEAS levels of the respective groups (corresponding to either sex) were not significant (Tables III and IV). However, on grouping in terms of the maturity of the cervix (ripe and unripe), the DHEAS levels of the respective groups indicated significant differences (Tables V and VI).

It was thus concluded that the stage of cervical dilatation was the determining factor, and the sex of the fetus was not a factor in causing significant differences between DHEAS levels.

Finally, according to our findings there were no significant chances in estradiol, estriol, and progesterone levels associated with the increase in cervical dilatation, and as was pointed out by Dr. Zuidema et al., the only significant increase was in the DHEAS levels.[2] It can thus be concluded that DHEAS is a hormone that increases during the dilatation period, which is the first stage of labor.

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Response declined

Critical comments on the treatment of tubal pregnancy with prostaglandins

To the Editors: The article by Egarter and Husslein (Egarter C, Husslein P. First successful intrauterine pregnancy after treatment of tubal pregnancy with prostaglandin $F_{2\alpha}$. AM J OBSTET GYNECOL 1989;161:904) describes the treatment of tubal pregnancy with prostaglandins as "highly encouraging." However, the associated burden and dangers for the patient are given little consideration. The injection of prostaglandin $F_{2\alpha}$ in a high dose (up to 10 mg) into the tube,[1] which has an increased blood circulation because of pregnancy, always presents the risk of mistaken intravascular administration that can have fatal results. Serious complications, in some cases fatal, have been reported after the use of intrauterine prostaglandin.[2] In addition, the injection of several milliliters of fluid into a tube already extended by the ectopic pregnancy increases the intratubal pressure and thus the danger of hematoma and tubal rupture. The subsequent 3-day systemic treatment with a prostaglandin E_2 derivative is not quite so dangerous; however, for the patient it is very unpleasant because of lower abdominal pain and other side effects such as nausea and vomiting. Because success of treatment can only be established after a few days, intensive care is necessary. At the same time, the uncertainty of the outcome presents a psychologic strain on the patient.

Considering the side effects already observed with this therapy such as hemodynamic disturbances, lung edema, and laryngospasm, it does not seem justifiable for the authors to evaluate the treatment as "having reduced postoperative morbidity." In the interest of patient safety, we consider it prudent to warn of the dangers of this method, especially when intensive care facilities are inadequate. There are currently other safer methods of treatment, for example, the laparoscopic salpingotomy, that guarantee certain termination of pregnancy without much stress for the patient, also providing a good chance for tubal patency.[3]

J. Dietl, MD, and T. H. Lippert, MD

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Reply

To the Editors: We appreciate the interest of Drs. Dietl and Lippert in our article and would like to address the points they raised in their letter. In the first patients treated with prostaglandins we also injected prostaglandin $F_{2\alpha}$ into the corpus luteum, assuming a direct luteolytic effect would occur. Severe side effects developed in three patients immediately after the intra*ovarian* application of prostaglandin $F_{2\alpha}$ and we indicated this fact by referring to the literature.[1] As soon

Table I. Prostaglandin $F_{2\alpha}$ treatment in patients with an initial β-subunit of human chorionic gonadotropin level <2500 mIU/ml (n = 120)

	No.	%
Success	101	84.2
Failure	19	15.8
Hysterosalpingogram (n = 40)		
Tubal patency	35	88
Tubal occlusion	5	12

as we omitted the intra*ovarian* prostaglandin $F_{2\alpha}$ dose and drew special attention to a slow application of the intra*tubal* dose with concomitant surveillance of blood pressure and heart frequency, no immediate adverse drug reactions occurred.

Drs. Dietl and Lippert stated that application of several milliliters of fluid might lead to tubal rupture caused by increased tubal pressure. The occurrence of this event is extremely unlikely because we only apply 1.5 to 2 ml; we never observed a single case with this side effect in our large series. Moreover, as Lang et al.[2] recently demonstrated, an intratubal instillation of up to 20 ml is apparently not associated with any such consequences.

It is true that the success of this treatment can only be established in some cases after a few days. Additional hormone parameters[3] and our growing experience will probably overcome this psychologic burden. However, other methods such as laparoscopic salpingotomy also do not guarantee definite termination of pregnancy as Vermesh et al.[4] showed with a 5.3% failure rate. In these cases the final resolution of ectopic pregnancy is not only delayed but also associated with a second operative procedure. Moreover, the laparoscopic management requires technical facilities as well as operative skills that are lacking in many gynecologic centers.

We believe that our final success rate of 84.2% in patients with an initial β-subunit of human chorionic gonadotropin level <2500 mIU/ml serum (Table I)[5] seems to justify the ongoing research with prostaglandin. The involved risks of the relatively simple application of prostaglandin $F_{2\alpha}$ are reasonable if our safety recommendations are used as follows: (1) aspiration *before* application to avoid erroneous intravasal injection, (2) strict supervision during application, (3) determinations of postoperative β-subunit of human chorionic gonadotropin values. Nonetheless, a prospective randomized comparison of prostaglandin treatment and laparoscopic operation would be of special interest.

Ch. Egarter, MD, and P. Husslein, MD

I. Department of Obstetrics and Gynecology, University of Vienna/Austria, Spitalgasse 23, A-1090, Vienna, Austria

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Ovulation prediction from cyclic changes in salivary electrical conductivity

To the Editors: To enable large-scale studies aimed at improvement of present diagnostic contraceptive methods, we have introduced luteinizing hormone (LH) determination in saliva and have shown a sufficiently reliable correlation between the salivary midcycle LH peak and ovulation confirmed by ultrasonography.[1-3] Unpublished data indicate a well-correlated relationship between cyclic changes in salivary electrical conductivity measured with a Philips conductometer and LH peaks. Albrecht et al.[4] have reported such a relationship for salivary electrical resistance and developed the CUE ovulation predictor for use in infertility treatment.[5-7] When a device that was easily handled became available for conductivity determination dissolved solids tester (DIST 4), it was tested together with the CUE for its potential in ovulation prediction. This letter reports on first results from 30 cycles comparing the data obtained with the CUE and the DIST.

For details regarding participants see Table I.

Basal body temperature was taken rectally with a mercury thermometer and the CUE and DIST were used immediately afterward. Only the oral CUE readings were taken. After this reading several milliliters of early morning saliva (i.e., before eating, drinking, smoking, etc.) were collected in a beaker fit to the sensor of the DIST and readings noted in the basal body temperature chart. Saliva was then transferred into plastic tubes and kept frozen until laboratory determination of LH. Salivary LH has been determined radioimmunologically by modifying a commercially available LH radioimmunoassay kit as previously described in detail.[1]

The CUE devices used in this study were purchased from Zetek, Inc. (Aurora, Colo.). The instrument measures salivary electrical resistance (ohm). A peak is said to occur 5 to 7 days before ovulation. The relevant peak is defined as a higher reading followed by at least two

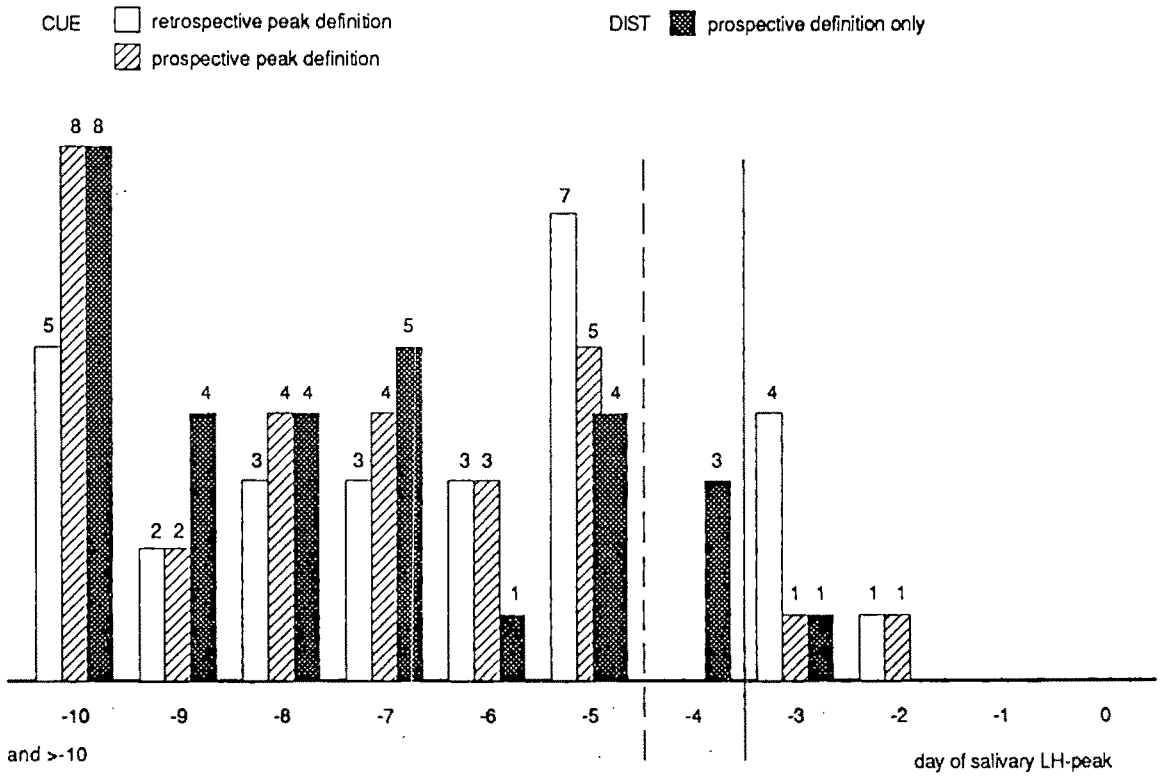


Fig. 1. Ovulation prediction in relation to salivary LH peak.

Table I. Participants and cycles

No. of nulliparous volunteers	*Age (yr)*	*No. of cycles*	*Cycle length (days)*	*Follicular phase (days)*	*Luteal phase (days)*
5	23.1 ± 2.95	30	29.7 ± 3.47	16.6 ± 2.86	13.1 ± 1.85

Table II. Predictive capacity of the CUE ovulation predictor and the DIST conductivity meter (N = 30)

	Cycles		*Ovulation prediction before salivary LH peak*			*Overall theoretical reliability (%)*	*Additionally diagnosed days of preovulatory infertility*
	Interpretable	*Not interpretable*	*≥5 days*	*4 days*	*≤3 days*		
CUE							
Retrospective peak definition	29	1	24	0	5	80	3.57 ± 2.63
Prospective peak definition	28	2	26	0	2	86.7	2.81 ± 1.92
DIST (only prospective peak definition)	30	0	26	3	1	96.7	2.86 ± 1.86

lower ones, the first one being at least 10% lower than the peak.

The DIST (World Precision Instruments, Inc., New Haven, Conn.) is a new pocket-size conductometer (microseconds). Results are displayed digitally as with the CUE. Total dissolved solids units are equivalent to parts per million of sodium chloride. For use in native saliva the DIST 4 (range 19,000 μs, resolution 100 μs,

accuracy 2%) proved to be appropriate. The testers were purchased from Austro-Merck (Vienna). No previous experience with this device exists in the field of our study.

Thirty cycles with complete data have been evaluated. With the retrospective definition for a CUE peak provided by the manufacturer an average of 3.57 ± 2.63 days of additional preovulatory infertility could be diagnosed. However, in six of 30 cycles (20%) infertility has been signaled for too long with regard for contraceptive purposes. In one case the CUE did not predict ovulation at all; in four cases the peak occurred only 3 days and in one case 2 days before the LH peak. In a search for a prospective rule for the CUE peak (e.g., as exceeding the mean by a certain margin), the range between 0.97 and 1.1 SDs above the mean was checked. Only a cutoff point of 0.97 gave reasonable results. With this altered rule for defining the peak as the first value above the mean + 0.97 SD, an additional 2.81 ± 1.92 days of preovulatory infertility could be diagnosed with four wrong indications: two predictions were too late and twice no peak was detectable.

Applying a similar peak rule to the DIST readings, interpretable results were obtained in all 30 cycles, and 2.86 ± 1.86 additional days of preovulatory infertility could be diagnosed. In only one case prediction came too late (day −3). Results are shown in Table II and Fig. 1.

As previously stated,[8] future fertility indicators should be able to predict ovulation at least 4 or 5 to 6 days in advance, taking into consideration the time sperm can retain their fertilizing capacity depending on the cervical factor.[9, 10] The reliability of a prediction 4 days before the salivary LH peak must be closely examined in field trials, although it has been reported as sufficient in the literature.[5, 6, 10, 11] We certainly do not believe that 3 days would be an adequate warning.[12]

The aim of the CUE is to predict the best time to conceive and is not to be used in contraception. The problem lies in the definition of the peak, which is only detectable 2 days *after* its occurrence. For contraceptive purposes the peak must be recognizable the very day it appears. We have tried to achieve this with a prospective concept which, however, yielded an overall theoretical reliability of only 86.7% (Table II). By contrast the DIST readings were interpretable in all 30 cycles, occurring too late in only one, thus resulting in a theoretical reliability of 96.7%. Whereas the numbers of additionally diagnosed preovulatory infertile days for the CUE and for the DIST are of the same order of magnitude, the substantial difference in the reliability of the devices allows only for the DIST to be considered for further investigation aimed at decisively improving diagnostic family planning methods. The underlying physiologic feature for the observed correlation between the DIST peaks and salivary LH peaks have not yet been fully explored, even though characteristic cyclic changes of salivary electrolytes are beyond doubt. Further studies with the DIST regarding the underlying mechanism and the reliability of predicting ovulation are currently under way in our laboratory.

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Amniotic fluid midtrimester delta optical density measurements at 450 nm in Rh disease

To the Editors: I read with interest the recent article by Ananth and Queenan (Ananth U, Queenan JT. Does

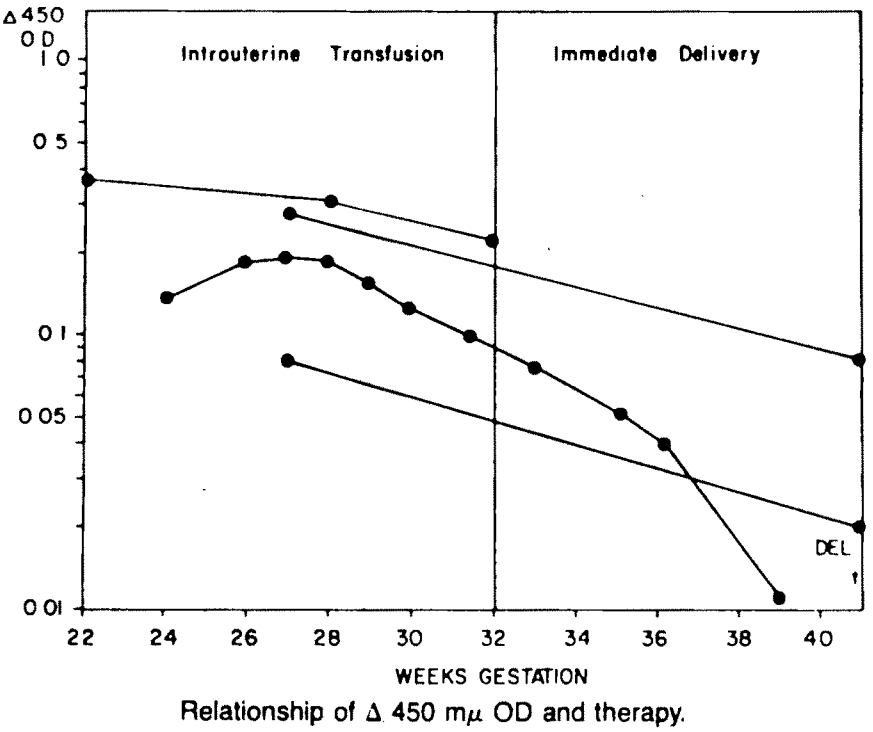


Fig. 1. Relationship between ΔOD_{450} and gestational age. Reprinted by permission from the *Southern Medical Journal* (1979;72:241-2).

midtrimester ΔOD_{450} of amniotic fluid reflect severity of Rh disease? AM J OBSTET GYNECOL 1989;161:47-9) regarding midtrimester amniotic fluid values of delta optical density measurements at 450 nm (ΔOD_{450}) in Rh disease. In their Fig. 1 they clearly show that in some patients the hemolytic process is under way between 16 and 20 weeks' gestation. However, I am a little disturbed by the statement that a single amniotic fluid ΔOD_{450} value >0.15 or an amniotic fluid trend rising above 0.15 indicates severe disease. In this study no ΔOD values are reported from unaffected pregnancies beyond 23 weeks' gestation.

I recommend that obstetricians exercise caution in the use of the cutoff point of 0.15 between 23 and 27 weeks' gestation. In 1979 I reported[1] two cases in which the ΔOD rose between 24 and 27 weeks' gestation from 0.140 to 0.200. A plot of the ΔODs of one patient is shown in Fig. 1. As you can see, the ΔOD plateaued at 27 to 28 weeks' gestation and then gradually declined to term. Both mothers were delivered of unaffected Rh-negative infants. Therefore I suggest that the recommendations of Ananth and Queenan not include the terminal weeks of the midtrimester.

George H. Nelson, PhD, MD

Department of Obstetrics and Gynecology, University of South Carolina, School of Medicine, Two Richland Medical Park, Suite 103, Columbia, SC 29203

REFERENCE

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Reply

To the Editors: In normal pregnancies (no erythroblastosis fetalis) the amniotic fluid delta optical density values at 450 nm (ΔOD_{450}) follows a rising trend from 16 to 23 weeks' gestation.[1,2] The values then level off. The normal amniotic fluid ΔOD_{450} values in the third trimester show a downward trend from week 27 until term. This trend forms the basis for the management for Rh disease in the third trimester. The accuracy of predicting severe Rh disease in the third trimester is excellent in our study and in others.[2,3,4] However, it has been shown in our study and in others[1,5] that Liley's graph cannot be extrapolated into the second trimester. Investigators have shown a poor correlation between amniotic fluid ΔOD_{450} values and the fetal hemoglobin in the midtrimester.[5] Therefore, some advocate the use of percutaneous umbilical blood sampling in all Rh-immunized pregnancies.[5]

This study pertains to amniotic fluid ΔOD_{450} values from 16 to 20 weeks' gestation. In the cases studied: a

value >0.15 was associated with severe erythroblastosis fetalis and values of <0.09 were associated with mild or no Rh disease. The ΔOD_{450} values between 0.09 and 0.15 require further evaluation to determine the trend.

Dr. Nelson comments that he has seen two patients in whom the amniotic fluid ΔOD_{450} ran between 24 and 27 weeks' gestation from 0.14 to 0.20. These infants were Rh-negative and unaffected.

We agree that >0.15 values are possible at that stage of pregnancy. Our study is focused on the period of 16 to 20 weeks' gestation when genetic amniocentesis is done. This is the time when normal physiologic fetal hemolysis is just beginning and the values are therefore lower.

Our recommendations do not pertain to the period between 21 and 27 weeks' gestation. And of course, Liley's graph works well thereafter.

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Books received

Acyclovir Therapy for Herpesvirus Infections. Edited by David A. Baker. 344 pages, illustrated. New York, 1990, Marcel Dekker, Inc. $99.75.

Adipose Tissue and Reproduction. Edited by R. E. Frisch. 142 pages, illustrated. Cambridge, 1990, S. Karger. $92.75.

Before Birth. Elena O. Nightingale, M.D., and Melissa Goodman. 111 pages, illustrated. Cambridge, Massachusetts, 1990, Harvard University Press. $22.50 ($8.95 soft cover).

Cellular and Molecular Events in Spermiogenesis. Edited by D. W. Hamilton and G. M. H. Waites. 334 pages, illustrated. New York, 1989, Cambridge University Press. $79.50.

Clinical Decisions in Obstetrics and Gynecology. Robert C. Cefalo. 377 pages, illustrated. Rockville, Maryland, 1990, Aspen Publishers, Inc. No price listed.

Gynecology for the House Officer. Edited by Stephen H. Cruikshank and Allan Chamberlain. 211 pages, illustrated. Baltimore, 1990, Williams & Wilkins. $16.95.

Health Care Standards 1990. Official Directory. ECRI. Plymouth Meeting, 1990. $245.

Health Technology Assessment: Methodologies for Developing Countries. Ronney B. Panerai and Jorge Pena Mohr. 109 pages, illustrated. Washington, 1989. Pan American Health Organization.

Infectious Diseases of the Female Genital Tract. Second Edition. Richard L. Sweet and Ronald S. Gibbs. 494 pages, illustrated. Baltimore, 1990, Williams & Wilkins. $67.50.

Infertility. Jan Rehiner. 128 pages. Toronto, 1989, Second Story Press. No price listed.

Infertility Surgery. John J. Stangel. 396 pages, illustrated. East Norwalk, Connecticut, 1990, Appleton & Lange. $78.00.

Maternal-Fetal Toxicology. Edited by Gideon Koren. 456 pages, illustrated. New York, 1990, Marcel Dekker, Inc. $125.00.

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Midlife and Older Women. AARP. 424 pages, illustrated. Washington D.C., 1989, Pan American Health Organization.

Obstetric Care: Standards of Prenatal, Intrapartum and Postpartum Management. Edited by Kathryn M. Andolsek. 293 pages, illustrated. Philadelphia, 1990, Lea & Febiger. $35.00.

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Practical Gynecologic Surgery. Mark E. Boyd. 257 pages, illustrated. Baltimore, 1989, Urban & Schwarzenberg. $59.50.

Principles and Practice of Clinical Gynecology. Edited by Nathan G. Kase, Allan B. Weingold, and David M. Gershenson. 1078 pages, illustrated. New York, 1990, Churchill Livingstone Inc. $74.50.

Quick Reference to OB-GYN Procedures. Third Edition. Hugh R. K. Barber, David H. Fields, and Sherwin A. Kaufman. 496 pages, illustrated. Philadelphia, 1990, J. B. Lippincott Company. $34.50.

Scarpelli: Pulmonary Physiology. Edited by Emile Scarpelli. 500 pages, illustrated. Philadelphia, 1990, Lea & Febiger. $89.50.

Sexually Transmitted Disease. Edited by Stephen A. Morse, Adele A. Moreland, and Sumner E. Thompson. 306 pages, illustrated. New York, 1990, J. B. Lippincott Company. $149.50.

Spermatozoa. Donald E. Tyler. 87 pages, illustrated. Ontario, Oregon, 1990, Discovery Books. $25.00.

Trichomonads Parasitic in Humans. Edited by B. M. Honigberg. 424 pages, illustrated. New York, 1989, Springer-Verlag. $129.00.

Vaginal Surgery. David H. Nichols and Clyde L. Randall. 463 pages, illustrated. Baltimore, 1989, Williams & Wilkins. $69.95.

Zuspan and Quilligan's Manual of Obstetrics and Gynecology. Second Edition. Jay D. Iams and Frederick P. Zuspan. 442 pages, illustrated. St. Louis, 1990, The C. V. Mosby Company. $24.95 (soft cover).

ITEMS

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George L. Hill, M.D.
Chairman OB/GYN Department
1000 North Oak Avenue
Marshfield, WI 54449
or call collect
(715) 387-5161

Marshfield Clinic

PERINATOLOGIST

A practice opportunity exists for a BC/BE Perinatologist to affiliate with a community teaching hospital in the Washington, D.C. suburbs. This hospital averages over 7000 deliveries annually and specialized in high risk OB.

Interested parties should submit a CV with requirements to:

Perinatologist Search Committee
1500 Forest Glen Road
Silver Spring, MD 20910

Postdoctoral Training Program in Medical Genetics

The Interdepartmental Medical Genetics Program at Stanford University School of Medicine provides advanced clinical and/or research training related to human inherited disease. Well-represented areas of the program include:

- The molecular basis of heritable disorders including polygenic and multifactorial diseases.
- Chromosome structure and function.
- Genome and gene mapping.
- The development of methods to manipulate and to study large fragments of DNA.
- Developing animal models and new treatment modalities of human genetic disease by homologous recombination.

Individuals with an MD, PhD, or equivalent degree are eligible for this three-year program which includes an extended period of research training with one of twenty-six training faculty and the opportunity to pursue applied training in clinical genetics, clinical cytogenetics, or molecular genetics in an ABMG-accredited setting. Minority individuals are especially encouraged to apply. For information and application forms, contact:

Uta Francke, M.D.
Departments of Genetics and Pediatrics
Howard Hughes Medical Institute
Stanford, California 94305-5428

FACULTY POSITIONS CALIFORNIA

LOS ANGELES COUNTY/ OLIVE VIEW MEDICAL CENTER

DIRECTOR OF MATERNAL- FETAL MEDICINE: Beautiful new state-of-the-art UCLA affiliated teaching hospital seeks director of a three-member division. Candidate should be a senior, experienced leader, board certified in maternal-fetal medicine, with investigative abilities. The position includes faculty appointment at UCLA School of Medicine.

GENERAL OBSTETRICIAN/GYNECOLOGIST: Board eligible/certified Obstetrician/Gynecologist to join twelve full-time hospital based academic physicians. Assignments include obstetrics, gynecology and outpatient services with emphasis on resident teaching/supervision. Clinical research encouraged. The position requires a faculty appointment at UCLA School of Medicine.

Olive View Medical Center is a 377-bed acute care facility located in the San Fernando Valley 25 miles north of the UCLA campus in Westwood. It serves a catchment population in excess of two million. It is an integral part of the UCLA student and residency training program in obstetrics and gynecology. Twelve obstetric and gynecology residents are assigned to Olive View. Over 7,000 high risk obstetrical patients are delivered yearly supported by a fully staffed antenatal testing unit, obstetrical anesthesia and neonatalogy/NICU coverage as well as full internal medicine, surgery, pediatrics and emergency medicine services.

Please apply with curriculum vitae to:
George Mikhail, M.D., Chairman
Department of Obstetrics and Gynecology
OLIVE VIEW MEDICAL CENTER
14445 Olive View Drive
Sylmar, CA 91342-1495

Equal Opportunity Employer M/F

OB/GYN WISCONSIN

Multi-specialty group in suburban Milwaukee seeks BC/BE Obstetrician/Gynecologist to join 6 physician OB/GYN department. Single site, single hospital practice. Competitive salary and fringe benefits. Forward inquiries and CV to:

Administrator
P.O. Box 427
Menomonee Falls, WI
53051

SUPERIOR PRACTICE OPPORTUNITY FOR A GYNECOLOGIST IN BEAUTIFUL, HISTORIC, CHARLESTON, SOUTH CAROLINA

A unique practice opportunity is available for a board certified GYNECOLOGIST to share office space with a well established, progressive (board certified) GYNECOLOGIC ONCOLOGIST.

- Well located, attractive office with common waiting room and business space with six (6) examining rooms and two physician's offices.
- Pleasant professional atmosphere.
- Shared on-call coverage available.
- Close proximity to two (2) JCAH accredited hospitals and Medical University.
- Located in Charleston, S.C., enjoy the cultural and recreational amenities of a cosmopolitan lifestyle, complimented by affordable housing, outstanding educational facilities, and a year round temperate climate.
- Near Kiawah, Seabrook, and Hilton Head Island Resorts.
- S.C. Malpractice rates lower than other areas.

To learn more about this unique practice opportunity, please call or forward your curriculum vitae to:

Myron Lutz, M.D.
1606 Ashley River Road
Charleston, S.C. 29407
803/556-4380

Finger Lakes Region Ithaca, New York

Unique opportunity for patient oriented physician in comprehensive OB-GYN service, building on established patient base of 6,000 patients. To include out-patient gynecology, obstetrics, surgery, infertility, and abortions. First call protection from nurse-midwives. Progressive university community (home of Cornell University) offers cultural attractions of a city with the benefits of small town living. Competitive salary, excellent benefits including malpractice. Summer/Fall 1991.

Send CV To: Joyce Leslie, M.D., Planned Parenthood of Tompkins County, 314 W. State St., Ithaca, NY 14850.

Planned Parenthood®
of Tompkins County

PERINATOLOGIST

Denver, Colorado

Rose Medical Center, Denver, Colorado is seeking a second BE/BC perinatologist to work full-time in a 400-bed private community hospital adjacent to the University of Colorado Health Sciences Center. With 3,600 deliveries per year, and 27 University Residents rotating through the department annually, Rose is the major private teaching affiliate of the University.

Responsibilities include, primary patient care, private consultation, physician, resident, and nursing education, clinical research, and a limited private practice in perinatology. This individual can expect frequent interaction with the Maternal/Fetal Division at the University of Colorado, and will be eligible for an appropriate clinical appointment at the University. All clinical responsibilities will be shared with the current full-time perinatologist at Rose. Additional call coverage is provided by other perinatologists in the Denver metro area.

A competitive salary guarantee is being offered, with excellent fringe benefits including malpractice insurance.

Qualified applicants, individuals completing fellowship in June, 1991, should forward CV's to:

Robert E. Wall, M.D., Chairman
Department of Obstetrics & Gynecology
Rose Medical Center
4567 East Ninth Avenue
Denver, Colorado 80220
Telephone: (303) 320-2077

THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY UNIVERSITY OF WISCONSIN MEDICAL SCHOOL MILWAUKEE CLINICAL CAMPUS

is seeking applicants for four (4) full-time faculty positions to participate in the development of a new women's health center and academic program.

Sinai Samaritan Medical Center is in the process of consolidating its obstetrical and gynecological services in a redesigned facility in downtown Milwaukee. The department supports a residency program, the largest perinatal service in Wisconsin (5200 deliveries), consultative ultrasound, genetic and infectious disease programs, and reproductive/endocrine services (including an IVF program). The department is affiliated with Planned Parenthooc of Wisconsin.

Qualifications include board candidacy or certification in obstetrics and gynecology and a commitment to teaching residents, medical students, and clinical research. Qualifications for the four positions for GENERAL OB/GYN can take into consideration special individual interests. Special expertise of interest for the department are:

— STATEWIDE FAMILY PLANNING AND AMBULATORY CARE (Part time medical director, Planned Parenthood)
— OPERATIVE LAPAROSCOPY, HYSTEROSCOPY
— UROGYNECOLOGY
— RESIDENT/MEDICAL STUDENT EDUCATION
— OB/GYN ULTRASOUND

Private practice opportunities are also available in an associated offsite multispecialty clinic and all facity members participate in a group practice at the location.

Contact: Fredrik F. Broekhuizen, M.D.
Chairman and Chief
Department of Obstetrics and Gynecology
University of Wisconsin Medical School
Sinai Samaritan Medical Center
Mount Sinai Campus
950 North 12th Street, G405
Milwaukee, WI 53233
(414) 283-7931

A full-time position is available in the Department of Obstetrics and Gynecology, University of California, Davis, Medical Center, Sacramento. Applicants should be Board eligible or certified in Obstetrics and Gynecology. Applicants must possess or be eligible for medical licensure in the State of California. Applicants must demonstrate experience and competence in teaching effectiveness and research related activities or potential for such activities.

Responsibilities of this position include inpatient and outpatient case management, participation in teaching activiteis with residents, interns and medical students, development and/or participation in research activities and involvement in University and Hospital committees.

Send curriculum vitae and five references to:

R. Jeffrey Chang, M.D.
Chairman, Department of Obstetrics
and Gynecology
University of California, Davis, Medical Center
1621 Alhambra Boulevard, Suite 2500
Sacramento, California 95816

The final date for receipt of applications is October 30, 1990.

The University of California, Davis is an equal opportunity, affirmative action employer.

FACULTY POSITION

GENERAL OBSTETRICIAN/ GYNECOLOGIST

The University of Louisville School of Medicine is seeking a Board eligible/certified general Obstetrician/Gynecologist. The University of Louisville serves metropolitan Louisville and the western one-half of Kentucky. This population provides a comprehensive base for research, education and community service. The candidate should display an interest in outpatient management systems as well as primary care aspects of Obstetrics and Gynecology. Excellent benefits and facilities. Send Curriculum Vitae to:

Stanley A. Gall, M.D.
Professor and Chairman
Department of Obstetrics
& Gynecology
University of Louisville
School of Medicine
Louisville, Kentucky 40292

UNIVERSITY OF OXFORD

NUFFIELD PROFESSORSHIP OF OBSTETRICS AND GYNAECOLOGY

The electors intend to proceed to an election to the Nuffield Professorship of Obstetrics and Gynaecology, which falls vacant on 1 October 1990, upon the retirement of Sir Alexander Turnbull. The stipend of the professorship is currently £41,025.

Applications (ten copies, or one from overseas candidates), naming three referees, should be received not later than 20 August 1990 by the Registrar, University Offices, Wellington Square, Oxford, OX1, 2JD, from whom further particulars may be obtained.

The University is an Equal Opportunity Employer

MATERNAL-FETAL MEDICINE

The Department of Obstetrics and Gynecology at the University of Tennessee Medical Center at Knoxville is currently recruiting one or two additional BC/BE specialists in Maternal-Fetal Medicine.

This is the chance to join a young, growing, dynamic program which encourages active participation in resident and outreach education and offers ample opportunity for basic and clinical research. More than 700 procedures are done monthly in the Department's autonomous Obstetrical Ultrasound and Antenatal Assessment Unit. Constuction of a new Labor and Delivery suite is expected to be completed in January of 1991.

A highly competitive compensation package, coupled with relatively low malpractice insurance, and proximity to many recreational facilities in beautiful East Tennessee makes this an extremely attractive opportunity for the person interested in combining a rewarding academic career and a full family life.

Academic rank is commensurate with qualifications and experience. Interested persons should send C.V. or inquiries to:

Kenneth F. Trofatter, Jr., MD, PhD
Associate Professor and Director
Maternal-Fetal Medicine
Department of Obstetrics & Gynecology

THE UNIVERSITY OF TENNESSEE
Medical Center at Knoxville
1924 ALCOA HIGHWAY
KNOXVILLE, TENNESSEE 37920
For more information call (615) 544-9300.
EEO/An Affirmative Action/Title IX/Section 504 Employer

OBSTETRICIAN/ GYNECOLOGIST

Board certified or board eligible obstetrician/gynecologist to join two member department in multispecialty clinic. Office ultrasound, colposcopy, and cryosurgery available. Adjacent to 94 bed community hospital with special care nursery.

Worthington, MN is a community of 11,000 located in the highly productive corn belt. Recreational activities include good hunting, fishing, and two 18 hole golf courses. Excellent schools, pollution free environment, with low crime rate make this an ideal community for family living.

Excellent compensation package available. Respond to Mr. John Sieve, Administrator, Worthington Medical Center, 508 10th Street, Worthington, MN 56187 or call 507-372-2921.

FACULTY POSITIONS FOR BOARD CERTIFIED OR ELIGIBLE

DIRECTOR, MATERNAL-FETAL DIVISION
PERINATOLOGIST
REPRODUCTIVE ENDOCRINOLOGIST
OB/GYN GENERALIST

These physicians will devote time to clinical practice, resident and medical student teaching programs and research.

Academic level will be in accordance with experience and achievement.

Excellent salary combines base-line and practice incentive plan plus a comprehensive benefit package.

Applicants should send curriculum vitae to:

John W. Greene, Jr., M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
University of Kentucky Medical Center
800 Rose Street, MN318
Lexington, KY 40536-0084

THE UNIVERSITY OF KENTUCKY IS AN AFFIRMATIVE ACTION, EQUAL OPPORTUNITY EMPLOYER AND ACTIVELY SEEKS THE CANDIDACY OF MINORITIES AND WOMEN.

OB/GYN

Located on **Lake Superior,** the largest freshwater lake in the world: Superior Memorial Hospital is seeking BE/BC OB/GYN physicians for this rural/city hospital/clinic based practice. 175K+ minimum net guarantee. New equipment; 24 hour anesthesiology coverage. Young, dynamic physician staff; friendly caring hospital staffing. Check out our lifestyle of year round recreational, fishing, hunting, outdoor, cultural and educational activities!!! Modern facility with 55 beds staffed, 161 beds licensed for this pregnant opportunity.

Call Collect: Jan Broad/Mel Fahs
Tel. 1-715-392-8281
Ext. 1109
Superior Memorial
Hospital
3500 Tower Ave.
Superior, WI 54880

CASE WESTERN RESERVE UNIVERSITY AND UNIVERSITY MACDONALD WOMENS HOSPITAL

1. Director, Division of Maternal-Fetal Medicine
2. Perinatologist with ultrasound/doppler experience
3. Gynecologic Oncologist
4. Ob/Gyn Generalist (2 Positions)

An outstanding and exciting opportunity exists for ob/gyns seeking full-time academic careers in one of the leading medical centers in the United States. The Department of Obstetrics and Gynecology at University Hospitals of Cleveland and Department of Reproductive Biology of Case Western Reserve University is under new leadership and is recruiting faculty to work in a University-affiliated, Level III hospital which is just completing the final phase of an extensive remodeling program. The positions include faculty appointments at the rank of Assistant, Associate or Full Professor, depending upon academic credentials. An excellent salary, incentive and benefit package is being offered. Board certified or eligible candidates should send their curriculum vitae to:

Wulf H. Utian, M.D., Ph.D.
Department of Ob/Gyn
University Hospitals of Cleveland
2074 Abington Road
Cleveland, OH 44106

The University and Hospital are equal opportunity, affirmative action employers, women and minorities are encouraged to apply.

STANFORD UNIVERSITY

The Department of Gynecology and Obstetrics is recruiting a faculty member at the level of Assistant or Associate Professor in the Medical Center Line of its professoriate. The position is for a generalist who also has a sub-interest (e.g., infectious disease, gyneco-urology, contraception). The successful candidate will have an established interest in the subdiscipline but will also participate in the obstetrics and gynecology services provided for HMO-based populations and provide consultative services. Opportunity for general Ob/Gyn practice/teaching is also available. Applicants must be Board Eligible or Certified and interested in teaching in a clinical setting.

Stanford University is committed to increasing representation of women and members of minority groups among its faculty and particularly encourages applications from such candidates.

Please send CV and names of three references to:

Mary Lake Polan, M.D., Ph.D.
Chairman, Search Committee
Department of Gynecology and Obstetrics
Stanford University Medical Center
Stanford, CA 94305-5317

MATERNAL-FETAL MEDICINE POSITIONS DEPARTMENT OF OBSTETRICS AND GYNECOLOGY UNIVERSITY OF ILLINOIS HOSPITAL CHICAGO, ILLINOIS

The Department of Obstetrics and Gynecology at the University of Illinois, Chicago, has two first year Fellowship positions available in Maternal-Fetal Medicine beginning July 1, 1991. This is a two-year accredited Fellowship program in which both clinical and research training are emphasized.

The Fellowship program at the University of Illinois Hospital and the affiliated Michael Reese Hospital is the largest perinatal clinical service in the City of Chicago, with more than 7000 deliveries per year, approximately 50% of which are high risk. There is an active prenatal genetic program including CVS. A large baboon colony is available for basic perinatal research. In addition to an active MD and clinical research faculty, the department employs basic science Ph.D. faculty. Residents who are interested in applying for the Fellowship should contact Andre Bieniarz, M.D., Director, Maternal-Fetal Medicine Fellowship, Department of Obstetrics and Gynecology, University of Illinois College of Medicine, 840 S. Wood Street, Chicago, IL 60612.

An affirmative action/equal opportunity employer.

The **Michael Reese Health Plan,** a large well-established HMO serving its members in 20 Health Centers throughout the Chicago Metro area, is seeking additional Board Certified/Eligible physicians in

Obstetrics Gynecology

Physicians with the Health Plan enjoy a full practice with modern facilities and equipment as well as opportunities for teaching. All specialty facilities available.

A highly-competitive salary and excellent benefits complement a rewarding practice and lifestyle.

Interested applicants should address inquiries to:

Alfred Kendrick, M.D.
Medical Affairs
MICHAEL REESE HEALTH PLAN
2545 King Drive, Chicago 60616
or call (312) 808-4551

Michael Reese Health Plan

an equal opportunity employer m/f/h

NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting for positions in our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

REPRODUCTIVE ENDOCRINOLOGIST

• SAN JOSE •

We are currently seeking a Reproductive Endocrinologist to establish and run a reproductive endocrinology subdivision in the department. Duties would include the full spectrum of reproductive endocrinology, outpatient and surgical management of infertility. Fellowship certification would be preferred. The department currently has 17 physicians and is still growing. We offer a generous benefits package including full coverage malpractice insurance. San Jose has beautiful weather and excellent access to Bay Area recreational and cultural activities.

For more information, please contact: Jerome L. Nehemiah, M.D., Chief, Department of OB/GYN, The Permanente Medical Group, Inc., 260 International Circle, Dept: AJOBG, San Jose, CA 95119, or call collect (408) 972-6180. EOE

KAISER PERMANENTE
Good People. Good Medicine.

PERINATOLOGIST

The Reading Hospital and Medical Center, a 625-bed teaching hospital with 2,400 deliveries per year, is seeking a Perinatologist to augment current genetics and perinatal service. With a 24-hour in-house obstetrical anesthesiology team and neonatology coverage, the Perinatologist would be Director of the Perinatal Service.

Responsibilities include residency teaching, supervision of antenatal testing unit, and consultations with private practitioners and some private practice. Close association with a University service for administrative and educational backup, coverage, and research involvement.

We offer a competitive salary with a comprehensive flexibly structured benefits package. Located in a desirable growth area in East Central PA, The Reading Hospital and Medical Center is a recognized leader in the delivery of health care and health care education. The community is an excellent place to raise a family with superb schools and varied recreational/cultural opportunities. The nearby metropolitan areas of New York City, Philadelphia and Baltimore/Washington, DC offer additional advantages. Interested candidates please submit curriculum vitae to:

Peter Schwartz, M.D.
Chairman, OB/GYN

THE READING HOSPITAL and MEDICAL CENTER
Reading, PA 19603
Equal Opportunity Employer m/f/h/v



OB/GYN BC/BE two positions available in Oklahoma for hospital based practice. New, fully equipped, LDRP facility, with central fetal monitoring, telemetry, dedicated staff and 24 hour obstetrical anesthesia and family prenatal classes. Level I and II nurseries, strong Pediatrician support. Progressive community with college, symphony and cultural opportunities. Malpractice rates reasonable. Salary and benefits guaranteed. Reply with CV to Medical Staff Office, Room 3122, P.O. Box 205, Oklahoma City, Oklahoma 73101.

OBSTETRICIAN GYNECOLOGIST

Western Massachusetts staff model Health Maintenance Organization is seeking two full-time, Board Certified/Board Eligible Obstetrician/Gynecologists to join our expert staff of five physicians and five midwives.

Our multi-specialty group practice employs 70 full-time physicians and provides care for a membership of over 65,000 patients in our modern suburban facilities. Inpatient care is provided at a 900-bed Tufts affiliated teaching hospital.

Attractive Pioneer Valley location with fine educational, cultural and recreational opportunities. Excellent salary and comprehensive benefit program. Please send curriculum vitae to: Oded Rencus, M.D., Chief of OB/GYN, 305 Bicentennial Highway, Springfield, MA 01118 or call (413) 594-3111.

MedicalWest
Community Health Plan
A BLUE CROSS & BLUE SHIELD HMO

We are an equal opportunity/affirmative action employer

OBSTETRICIAN/ GYNECOLOGIST

Immediate opening for a Board Certified/Eligible physician to work with 5 others at a well-established, growing HMO. Rochester Medical Group is a multispecialty medical group practice serving 45,000 patients at multiple sites. Clinical faculty appointment at the University of Rochester is available with this position. Competitive salary/ benefits with opportunities for research and resident teaching. Send resume to:

Patricia Hosking
Rochester Medical Group, PC
1800 Hudson Avenue
Rochester, NY 14617

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
Medical Department

The M.I.T. Medical Department is seeking a full-time Obstetrician/Gynecologist or a part-time Gynecologist. Applicants must be board certified or qualified. The Medical Department is a multi-specialty group practice of 24 full-time and more than 40 part-time physicians currently providing care to 30,000 patients including students, employees and their families, largely through prepaid comprehensive health plans. Salary is competitive, and benefits are excellent. The Massachusetts Institute of Technology is an Equal Opportunity/ Affirmative Action Employer. Women and members of minorities are urged to apply. M.I.T. is a non-smoking environment.

Send inquiries and C.V. to Arnold N. Weinberg, M.D., Medical Director, M.I.T. Medical Department, E23-279, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139.

OB/GYN
Northeastern Wisconsin

18 physician multi-specialty group located in a medium-sized Lake Michigan community seeks a second and third BC/BE physician to join its department of Obstetrics and Gynecology. Positions offer an excellent professional, financial and life-style opportunity. Send C.V. or call James Robinson, Administrator, Manitowoc Clinic, 601 Reed Avenue, Manitowoc, WI 54220. Telephone: (414) 682-8841.

Obstetrics/ Gynecology

WISCONSIN: Marshfield Clinic, a multi-specialty group practice with 350 physicians is seeking BE/BC obstetricians/gynecologists to join expanding (40-50 physician) regional centers in Chippewa Falls and Woodruff, Wisconsin. A third OB/GYN is needed for each facility. Chippewa Falls is located 1 1/2 hours from downtown Minneapolis/St. Paul and twenty minutes from a major four year campus of the University of Wisconsin. Known as the "Lakeland Area" (over 1,000 navigable lakes) Woodruff is truly one of the most attractive vacation areas in the upper Midwest and renown for its year-round outdoor recreational activities. Both communities offer exceptional recreational, cultural, and educational opportunities. An emphasis on quality practice and life-style is combined with a total compensation package on reaching membership in excess of $200,000. Starting salary negotiable. Fringe benefit package outstanding; includes self-insured malpractice. No start-up expense. Send C.V. and references to:

David L. Draves
Director, Regional Development
1000 North Oak Avenue
Marshfield, Wisconsin 54449
or call collect at
(715)387-5376

Marshfield Clinic

Join us.

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND, a 375,000-member prepaid group practice, currently has a position available for an Obstetrician/Gynecologist. We are a multi-specialty organization located in the scenic Seattle area.

To inquire, write to:
Manager, Medical Staff Personnel
Group Health Cooperative
of Puget Sound
521 Wall Street
Seattle, WA 98121

Group Health Cooperative
of Puget Sound
Affirmative Action/Equal Opportunity Employer

Fargo Clinic
MeritCare

OB-GYN

Large multispecialty group is seeking BC/BE Obstetrician-Gynecologist to join seven member department. Department is active in donor and husband insemination. Opportunity to develop Invitro and Gift Programs available.

Fargo Clinic is a 250 physician group that practices in 30 locations throughout eastern ND and western MN. The main facility is located next to St. Luke's Hospitals, a 400 bed tertiary care & trauma center. St. Luke's is a NACHRI designated Children's Hospital with a level III ICN.

Fargo-Moorhead is a tri-college community of 130,000 located just minutes from the lake country of western Minnesota. Abundant cultural, recreational, sporting and hunting activities available year around.

Outstanding compensatory package available. Respond to Robert C. Montgomery, M.D., Chairman, Physician Recruitment, 737 Broadway, Fargo, ND 58123.

BRIGHAM AND WOMEN'S HOSPITAL

Obstetrician/Gynecologist

The Brigham and Women's Hospital, a major teaching hospital of Harvard Medical School, seeks several obstetrician/gynecologists to join a busy full-time faculty group practice in general obstetrics and gynecology. The practice is located in a private setting near the hospital.

Applicants should be Board-certified/eligible.

Academic appointment at Harvard Medical School will be granted.

Offers competitive economic package and generous fringe benefits.

Commitment to clinical care and teaching are essential.

Send inquiry and curriculum vitae to:

Kenneth J. Ryan, M.D.
Chairman
Department of Obstetrics and Gynecology
Brigham and Women's Hospital
75 Francis Street, ASB1-3-073
Boston, MA 02115

The Brigham and Women's Hospital is an affirmative action, equal opportunity employer.

FACULTY POSITION
DIVISION OF MATERNAL-FETAL MEDICINE
ALBANY MEDICAL COLLEGE

Rapidly expanding division in our Department of Ob/Gyn needs a third board eligible/certified individual. Candidates should have a strong background in obstetric ultrasound as well as a commitment for medical student and resident education. Protected time for research and other academic pursuits guaranteed. New facility nearing completion. Academic rank in accordance with experience. Competitive salary plus attractive faculty incentive plan provided.

Albany, capital of New York State, offers major cultural and recreational opportunities as well as a variety of life styles in a sane environment. INTERESTED CANDIDATES SHOULD SEND A LETTER OF INTEREST WITH CV TO:

Myron Gordon, M.D.
Chairman, Department of OB/GYN
Albany Medical College A-74
47 New Scotland Avenue
Albany, New York 12208
OR
Paul J. Weinbaum, M.D.
Head, Division of Maternal-Fetal Medicine
Department of OB/GYN A-133

BC/BE Obstetrician/Gynecologist opportunities available. Join an independent, multispecialty group with 10 clinic locations in the Minneapolis/St. Paul metropolitan area. Full range of obstetrics and gynecology including: high risk obstetrics, obstetric anesthesia, immediate care of newborns, gyn oncology, gyn surgical pathology, reproductive endocrinology, infertility, non-surgical management of breast disease, family planning, emergency medicine, psychosexual and psychosomatic counseling, genetics, medical jurisprudence, and the full range of commonly accepted diagnostic procedures.

MD required plus 4 years training in ob/gyn residency. Salary beginning at $110,000 annually, excellent benefit package, required 20 clinic hours per week.

Call or send curriculum vitae to:

Maureen Reed, MD, Chief of Staff
Aspen Medical Group
Administration Department (nab)
1020 Bandana Boulevard W
St. Paul, MN 55108
(612) 641-7185

OBSTETRICIAN/ GYNECOLOGIST
UPSTATE NEW YORK

Private Practitioner urgently needed for Auburn, in the beautiful Fingerlakes area of Central New York. Many benefits including income guarantee. The area is notorious for its numerous recreational opportunities, excellent school system, low crime rate, and quality life environment. Good coverage system; affiliated with a modern, progressive hospital. Proximity to metropolitan areas of Syracuse and Rochester. Forward C.V.'s or requests for more information to:

Pat Nervina, Assistant Administrator
Auburn Memorial Hospital
Auburn, New York 13021
(315) 255-7224

OBSTETRICS & GYNECOLOGY

Obstetrician/Gynecologist needed to join a five physician department at a major regional multispecialty clinic in Billings, Montana. Clinic setting includes all specialties and is adjacent to an outstanding tertiary care referral hospital. Excellent opportunity for a top notch board eligible or board certified Obstetrician/Gynecologist looking for a challenging practice in a geographic area offering unlimited recreational potential. Those interested send CV to:

John W. Heizer, M.D.,
Medical Director
The Billings Clinic
P.O. Box 35100
Billings, Montana 59107-5100

OBSTETRICIAN-GYNECOLOGIST

Kalamazoo, Michigan

Bronson Hospital is currently seeking BE/BC OB/GYNs to join group of 3 hospital-based OB/GYNs. An impressive salary, health insurance, malpractice insurance and moving expenses are being offered.

Bronson Methodist Hospital, a 442 bed teaching facility, is southwestern Michigan's Perinatal Center. Virtually every medical specialty is represented within the 550 member medical staff including 25 OB/GYNs, 6 neonatologists and 2 perinatologists.

Kalamazoo, a university community with a metropolitan population of 220,000, is 135 miles between Chicago and Detroit offering diverse cultural and recreational activities. Lake Michigan is only 30 miles away and many ski resorts are easily accessible. Public, private and parochial schools are recognized for their academic excellence. Kalamazoo County is economically diversified and home for The Upjohn Company's international headquarters.

For more information about this practice opportunity, please send CV or call:

Debra Hartman
Bronson Healthcare Group
One Healthcare Plaza
Kalamazoo, Michigan 49007
(800) 594-9022
(616) 341-6331

Columbia University

The Dept. of OB/GYN at Harlem Hospital Center, an affiliate of Columbia University, has the following full time opportunities available:

Perinatologist

Candidates must be board certified in OB/GYN and board certified or eligible in Perinatology.

Oncologist

Candidates must be board certified in OB/GYN and board certified or eligible in Oncology.

General OB/GYN

Several positions available for full-time Obstetricians/Gynecologists. Applicants must be board certified or eligible in OB/GYN.

Faculty appointments will be at the level of Instructor or Asst. Clinical Professor, contingent upon experience and credentials. Please apply to: Sterling B. Williams, MD, Director, Dept. of OB/GYN, Harlem Hospital Center, 506 Lenox Avenue, New York, NY 10037. Columbia University takes affirmative action to ensure equal opportunity.

Harlem Hospital Center
A Member of N.Y.C. Health and Hospitals Corp.

CHAIR
DEPARTMENT OF OBSTETRICS/ GYNECOLOGY
JAMES H. QUILLEN COLLEGE OF MEDICINE
EAST TENNESSEE STATE UNIVERSITY

Candidates are being sought for the position of Chair of the Department of Obstetrics/Gynecology, James H. Quillen College of Medicine, East Tennessee State University, a community-based medical school which graduated its ninth class in May 1990. The Department currently has 12 full-time faculty, active research programs, an established faculty practice plan which includes the subspecialities of maternal fetal medicine and reproductive endocrinology. It also includes 30 part-time and volunteer faculty in this and neighboring communities. The Department has significant teaching responsibilities in undergraduate, graduate, and continuing medical education. The College of Medicine is located in a prosperous, beautiful Southern Appalachian Mountain community, with a population base of over one million in the immediate referral area. Candidates must be board certified in Obstetrics and Gynecology with proven expertise in teaching, research, and administration. Interested applicants should contact Steven L. Berk, M.D., Chairman, Obstetrics/Gynecology Search Committee, Department of Internal Medicine, P. O. Box 21,160A, Johnson City, Tennessee 37614, (615) 929-6282. ETSU is an AA/EOE.

ELKO REGIONAL MEDICAL CENTER

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OBSTETRICIAN/GYNECOLOGIST

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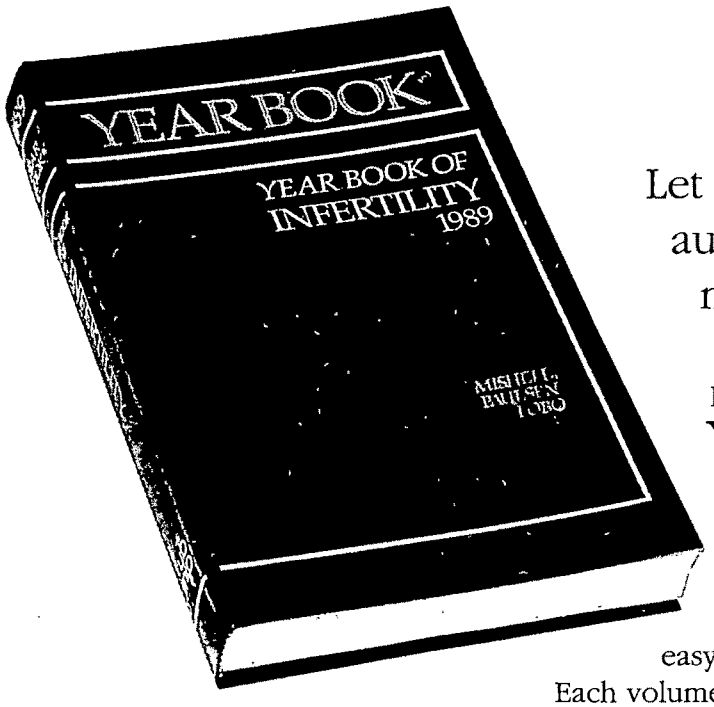
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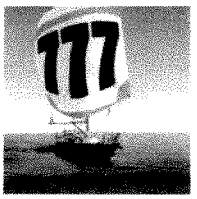
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The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this brief summary is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined. Throughout this brief summary epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods. 1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. a. Myocardial Infarction. An increased risk of myocardial infarction has been associated with oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives. Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors. b. Thromboembolism. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed. c. Cerebrovascular diseases. Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users, for both types of strokes, and smoking interacted to increase the risk of stroke. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. d. Dose-related risk of vascular disease from oral contraceptives. A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptive. The activity and amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen. e. Persistence of risk of vascular disease. There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens. 2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE. One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. However, smokers 35 and older and non-smokers 40 and older who use oral contraceptives have a significant increase in mortality higher than those using other methods of birth control. These facts must be weighed in conjunction with failure rates for other methods and the risk associated with subsequent pregnancy. 3. CARCINOMA OF THE REPRODUCTIVE ORGANS. Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. While there are conflicting reports most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. 4. HEPATIC NEOPLASIA. Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. 5. OCULAR LESIONS. There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately. 6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY. Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out. 7. GALLBLADDER DISEASE. Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens. 8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users. This effect has been shown to be directly related to estrogen dose. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives. A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users. 9. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with extended duration of use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity. Women with a history of hypertension or hypertension-related diseases, or renal disease, should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users. 10. HEADACHE. The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause. 11. BLEEDING IRREGULARITIES. Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent. 12. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. **PRECAUTIONS:** 1. PHYSICAL EXAMINATION AND FOLLOW UP. A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. 2. LIPID DISORDERS. Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. 3. LIVER FUNCTION. If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function. 4. FLUID RETENTION. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. 5. EMOTIONAL DISORDERS. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 6. CONTACT LENSES. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. 7. DRUG INTERACTIONS. Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines. 8. INTERACTIONS WITH LABORATORY TESTS. Certain endocrine and liver function tests and blood components may be affected by oral contraceptives: a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability. b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radio-immunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. c. Other binding proteins may be elevated in serum. d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids, however, free or biologically active levels remain unchanged. e. Triglycerides may be increased. f. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives. 9. CARCINOGENESIS. See WARNINGS section. 10. PREGNANCY. Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections. 11. NURSING MOTHERS. Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child. **INFORMATION FOR THE PATIENT: See Patient Package Insert.**

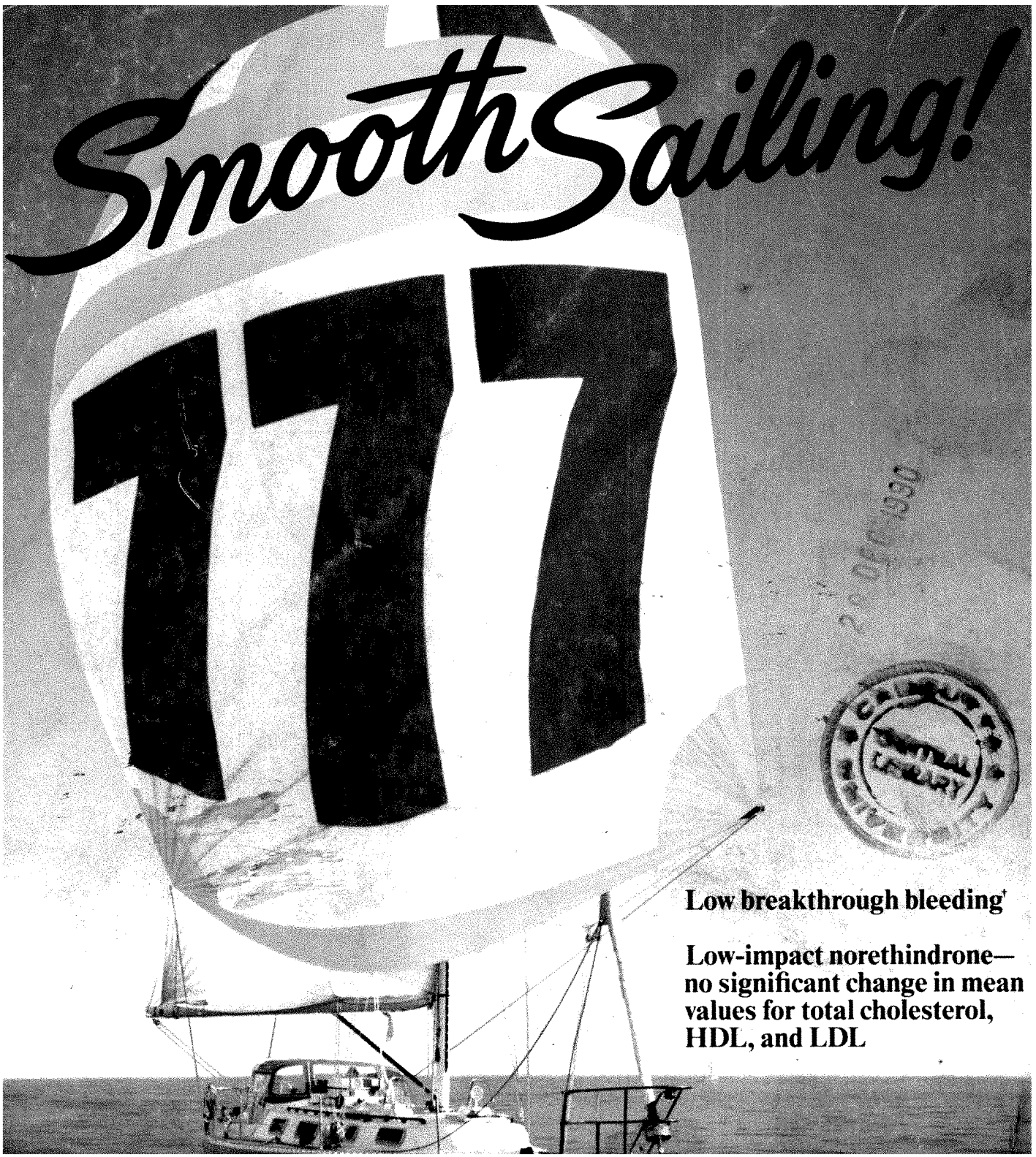
ADVERSE REACTIONS: An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section). Thrombophlebitis and venous thrombosis with or without embolism. Arterial thromboembolism. Pulmonary embolism. Myocardial infarction. Cerebral hemorrhage. Cerebral thrombosis. Hypertension. Gallbladder disease. Hepatic adenomas or benign liver tumors. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea. Vomiting. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Amenorrhea. Temporary infertility after discontinuation of treatment. Edema. Melasma which may persist. Breast changes: tenderness, enlargement, secretion. Change in weight (increase or decrease). Change in cervical erosion and secretion. Diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome. Cataracts. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. Hemolytic uremic syndrome. Acne. Changes in libido. Colitis.

OVERDOSAGE: Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

Revised 9/89

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Raritan, NJ 08869-0602

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Smooth Sailing!
777
Low breakthrough bleeding†
Low-impact norethindrone—no significant change in mean values for total cholesterol, HDL, and LDL

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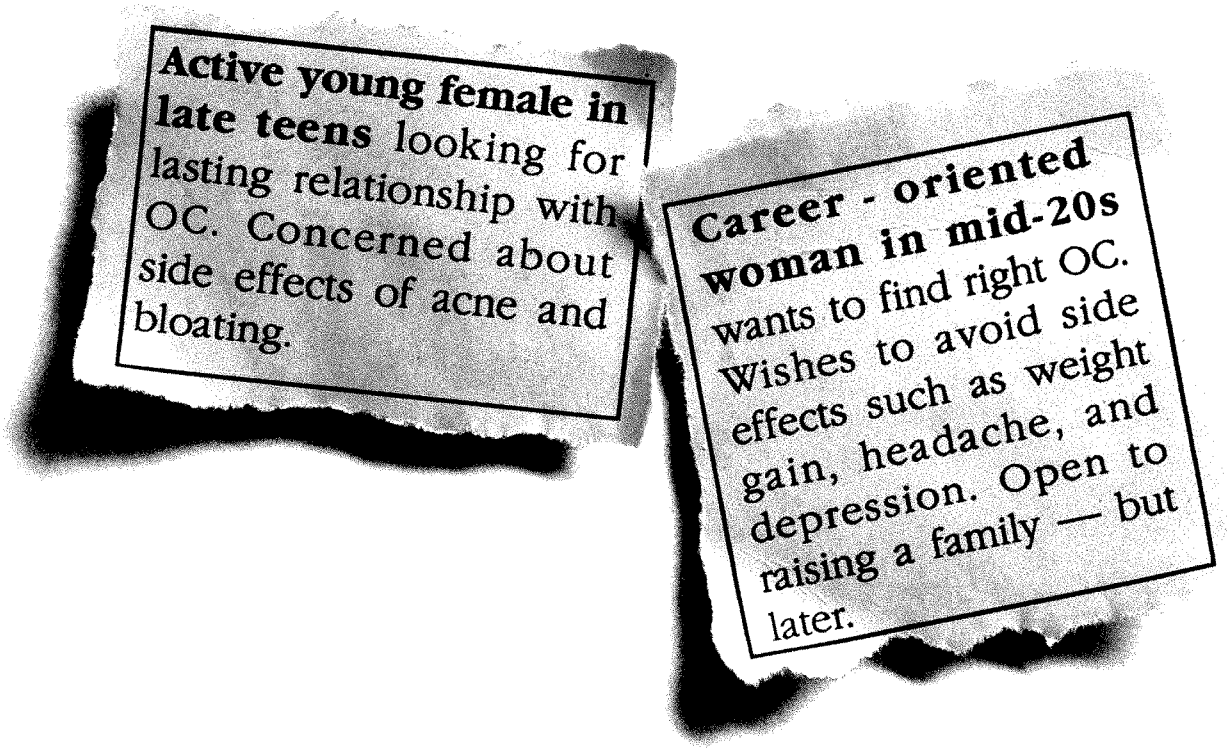
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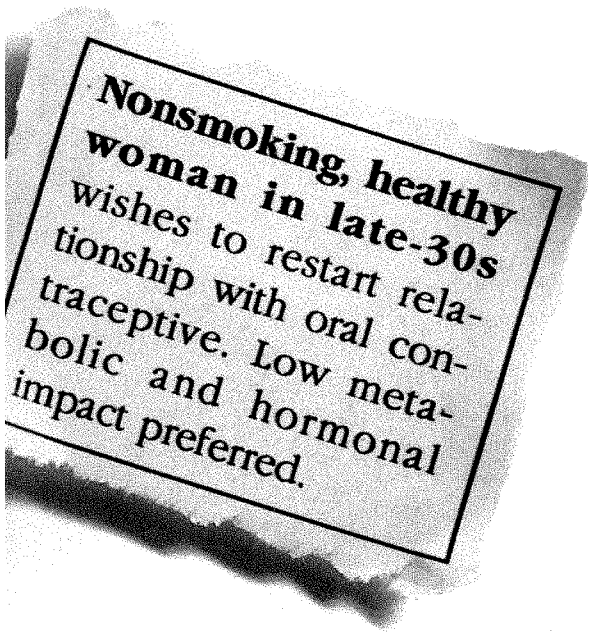
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Active young female in late teens looking for lasting relationship with OC. Concerned about side effects of acne and bloating.
Career - oriented woman in mid-20s wants to find right OC. Wishes to avoid side effects such as weight gain, headache, and depression. Open to raising a family — but later.



A personalized approach to oral contraceptives.

Because Tri-Norinyl is uniquely phased for all phases of a woman's reproductive life, it's ideal for a wide range of patient types:

Older, nonsmoking patients restarting contraception, because Tri-Norinyl is the only multiphasic with low-impact norethindrone that *lowers* progestin in late cycle to minimize overall hormonal and metabolic impact.

Career-oriented patients delaying childbearing, because reduced progestin helps minimize side effects that can disrupt daily life, such as weight gain, headache, and depression.

Younger patients just starting contraception, because low-impact norethindrone lowers the risk of acne and bloating, and is increased at mid-cycle, to provide enhanced endometrial support when breakthrough bleeding is most likely to occur.

(NORETHINDRONE AND ETHINYL ESTRADIOL) TABLETS

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Committed to the OB/GYN and women's healthcare

SYNTEX

SYNTEX LABORATORIES, INC
PALO ALTO, CA 94304

Serious as well as minor side effects have been reported following the use of all oral contraceptives. These include thromboembolic disease.
Please see next page for brief summary of prescribing information. © 1990 Syntex Laboratories, Inc. 814-H2-172-90

TRI-NORINYL®

(NORETHINDRONE AND ETHINYL ESTRADIOL) TABLETS

BRIEF SUMMARY

TRI-NORINYL® 21-Day Tablets (7 blue tablets of norethindrone 0.5 mg with ethinyl estradiol 0.035 mg, 9 yellow-green tablets of norethindrone 1.0 mg with ethinyl estradiol 0.035 mg, 5 blue tablets of norethindrone 0.5 mg with ethinyl estradiol 0.035 mg)
TRI-NORINYL® 28-Day Tablets (7 blue tablets of norethindrone 0.5 mg with ethinyl estradiol 0.035 mg, 9 yellow-green tablets of norethindrone 1.0 mg with ethinyl estradiol 0.035 mg, 5 blue tablets of norethindrone 0.5 mg with ethinyl estradiol 0.035 mg, 7 inert orange tablets)
BREVICON® 21-Day Tablets (norethindrone 0.5 mg with ethinyl estradiol 0.035 mg)
BREVICON® 28-Day Tablets (21 norethindrone 0.5 mg with ethinyl estradiol 0.035 mg tablets followed by 7 inert tablets)
NORINYL® 1 + 35 21-Day Tablets (norethindrone 1 mg with ethinyl estradiol 0.035 mg)
NORINYL® 1 + 35 28-Day Tablets (21 norethindrone 1 mg with ethinyl estradiol 0.035 mg tablets followed by 7 inert tablets)
NORINYL® 1 + 50 21-Day Tablets (norethindrone 1 mg with mestranol 0.05 mg)
NORINYL® 1 + 50 28-Day Tablets (21 norethindrone 1 mg with mestranol 0.05 mg tablets followed by 7 inert tablets)
NOR-Q.D.® (norethindrone) Tablets 0.35 mg
ORAL CONTRACEPTIVE (O.C.) AGENTS

Indications: Prevention of pregnancy.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who have the following conditions:
- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium, and known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas, carcinomas or benign liver tumors
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, hypercholesterolemia, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations containing 0.05 mg or higher of estrogen. The effects of long term use with lower dose formulations of both estrogens and progestogens remain to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease. Relative risk, the *ratio* of the incidence of a disease among oral contraceptive users to that among non-users cannot be assessed directly from case control studies, but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6. The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women 35 or older, with smoking accounting for the majority of excess cases.

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors for coronary artery disease, such as hypertension, diabetes, hyperlipidemias, hypercholesterolemia, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and impair oral glucose tolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see **WARNINGS**, section 9). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. One cohort study has shown the relative risk to be somewhat lower, about 3 for new cases (subjects with no past history of venous thrombosis or varicose veins) and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A 2- to 6-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery and during and following prolonged immobilization. Since the immediate postpartum period also is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular diseases

An increase in both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. In general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users for both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk also is greater in women 35 or older and among smokers.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with some progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content that produces satisfactory results for the individual.

e. Persistence of risk of vascular disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. Subarachnoid hemorrhage also has a significantly increased relative risk after termination of use of oral contraceptives. However, these studies were performed with oral contraceptive formulations containing 0.05 mg or higher of estrogen.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. However, smokers 35 and older and non-smokers 40 and older who use oral contraceptives have an increase in mortality greater than those using other methods of birth control. These facts must be weighed in conjunction with failure rates for other methods and the risk associated with subsequent pregnancy.

3. CARCINOMA OF THE BREAST AND REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone study also showed no latent effect on the risk of breast cancer for at least a decade following long term use. A few studies have shown a slightly increased relative risk of developing breast cancer, although the methodology of these studies, which included differences in examination of users and non-users and differences in age at start of use, has been questioned.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast or cervical cancers, a cause and effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is less than 1 per 1,000,000 users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. More recent studies do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to impair oral glucose tolerance. Oral contraceptives containing greater than 0.075 mg of estrogen cause glucose intolerance with impaired insulin secretion, while lower doses of estrogen may produce less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS**, sections 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives. The incidence of risk also was reported to increase with continued use and among older women. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. PHYSICAL EXAMINATION AND FOLLOW-UP

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines.

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. CARCINOGENESIS

See **WARNINGS** section.

10. PREGNANCY

Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

INFORMATION FOR THE PATIENT

See **PATIENT LABELING**.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section):

• Thrombophlebitis • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas, carcinomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

• Mesenteric thrombosis • Retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

• Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema • Melasma which may persist • Breast changes: tenderness, enlargement, secretion • Change in weight (increase or decrease) • Change in cervical erosion and secretion • Diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine • Rash (allergic) • Mental depression • Reduced tolerance to carbohydrates • Vaginal candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

• Pre-menstrual syndrome • Cataracts • Changes in appetite • Cystitis-like syndrome • Headache • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Vaginitis • Porphyria • Impaired renal function • Hemolytic uremic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:

• Increased menstrual cycle regularity • Decreased blood loss and decreased incidence of iron deficiency anemia • Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:

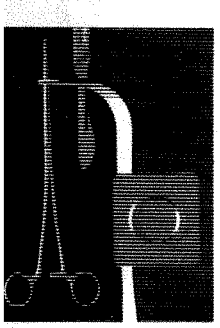
• Decreased incidence of functional ovarian cysts • Decreased incidence of ectopic pregnancies

Effects from long-term use:

• Decreased incidence of fibroadenomas and fibrocystic disease of the breast • Decreased incidence of acute pelvic inflammatory disease • Decreased incidence of endometrial cancer • Decreased incidence of ovarian cancer

Rev. August 1989

SYNTEX



Count on

CEFOTAN® IM/IV
(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

Intravenous or Intramuscular Use
EF SUMMARY

ICATIONS AND USAGE
:ATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the wing infections when caused by susceptible strains of the designated organisms:
ıary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus ıbilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia ɣeri,* and *Morganella morganii*).
er respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *ɔhylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* luding ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*
ı and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* cies (excluding enterococci), and *E coli.*
ecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, ratus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *tococcus* and *Peptostreptococcus* species*).
a-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, ɐetaiotaomicron*).
e and joint infections caused by *Staphylococcus aureus.**
icacy for this organism in this organ system was studied in fewer than ten infections.
pecimens for bacteriological examination should be obtained in order to isolate and identify sative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted ıre results of susceptibility studies are known; however, once these results become available, the biotic treatment should be adjusted accordingly.
cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other ous infections in which the causative organism has not been identified, it is possible to use CEFOTAN comitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown e synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. dosage recommended in the labeling of both antibiotics may be given and depends on the severity ıe infection and the patient's condition.
E: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully ıitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is onged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. ough, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that hrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
IPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain ıoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transhral surgery, biliary tract surgery, and gastrointestinal surgery).
ıe prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In pats undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping ıe umbilical cord.
there are signs and symptoms of infection, specimens for culture should be obtained for identifica- of the causative organism so that appropriate therapeutic measures may be initiated.
ITRAINDICATIONS
OTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.
ıINGS
ıre therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the ent has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, ıcillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. biotics should be administered with caution to any patient who has demonstrated some form of ɣy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. ous acute hypersensitivity reactions may require epinephrine and other emergency measures. eudomembranous colitis has been reported with the use of cephalosporins (and other broad-ɛtrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop rhea in association with antibiotic use.
eatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overvth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of biotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. ild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be ıaged with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not reıd by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for anti-c-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.
CAUTIONS
IERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overvth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection s occur during therapy, appropriate measures should be taken.
common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in hrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutrial state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at and exogenous vitamin K administered as indicated.
:FOTAN should be used with caution in individuals with a history of gastrointestinal disease, pararly colitis.
ORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction 'acterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, ı is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the stion of alcoholic beverages following the administration of CEFOTAN.
IG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given e, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an ıoglycoside.
IG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur Benedict's or Fehling's solution.
ı with other cephalosporins, high concentrations of cefotetan may interfere with measurement of ım and urine creatinine levels by Jaffe reaction and produce false increases in the levels of tinine reported.
CINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in ıals have not been performed to evaluate carcinogenic potential, no mutagenic potential of tetan was found in standard laboratory tests.
ɛfotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

CEFOTAN® (cefotetan disodium)

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.
Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.
USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.
DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.
IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.
Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.
When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.9 × value for males

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.
HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.
1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

Manufactured for

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Rev. I 11/88 63985-01

Cefotan arithmetic.

CEFOTAN IV 2g, q12h + doxycycline IV or PO 100 mg, q12h

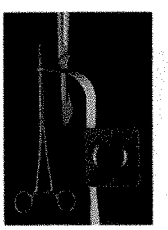
•CDC• CENTERS FOR DISEASE CONTROL RECOMMENDED FOR PID[7]

+ more cost-effective than cefoxitin[1,2]

− less frequent dosing than cefoxitin[3,4]

× several times the half-life of cefoxitin[5,6]

= single-dose prophylaxis/ twice-daily treatment



Count on

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In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, Briceland LL, Cooper B. The conversion of cefoxitin usage to cefotetan: an interdisciplinary approach. *Am J Surg.* 1988; 155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT. Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg.* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference* ed 43. Oradell, NJ: Medical Economics Co; 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH. Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg.* April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, Outman WR, Deckers PJ, Martens MG. Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg.* 1988;155(5A):67-70. **7.** Centers for Disease Control. 1989 Sexually Transmitted Diseases Treatment Guidelines. *MMWR.* 1989;38(suppl S-8):1-43.

Please see adjacent page for brief summary of prescribing information.

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This issue contains Transactions of the Tenth Annual Meeting of the Society of cians and Transactions of the Fifty-second Annual Meeting of the South Atlantic stetricians and Gynecologists beginning on page 1000.

TRANSACTIONS OF THE TENTH ANNUAL MEETIN SOCIETY OF PERINATAL OBSTETRICIANS

Metabolism of cocaine by human placentas: Implications for fetal exposure

Daniel A. Roe, BS, Bertis B. Little, PhD, Roger E. Bawdon, PhD, and Larry C. G
Dallas, Texas

Human placental microsomes metabolized cocaine in vitro, suggesting a protective maternal-fetal physiology.

Survival rates of monoamniotic twins do not decrease after 30 w gestation

Stephen R. Carr, MD, Michael P. Aronson, MD, and Donald R. Coustan, MD
Providence, Rhode Island

An advantage to early delivery in monoamniotic twin pregnancies could not be dem because fetal survival rates in 24 sets of monoamniotic twins did not decrease after gestation.

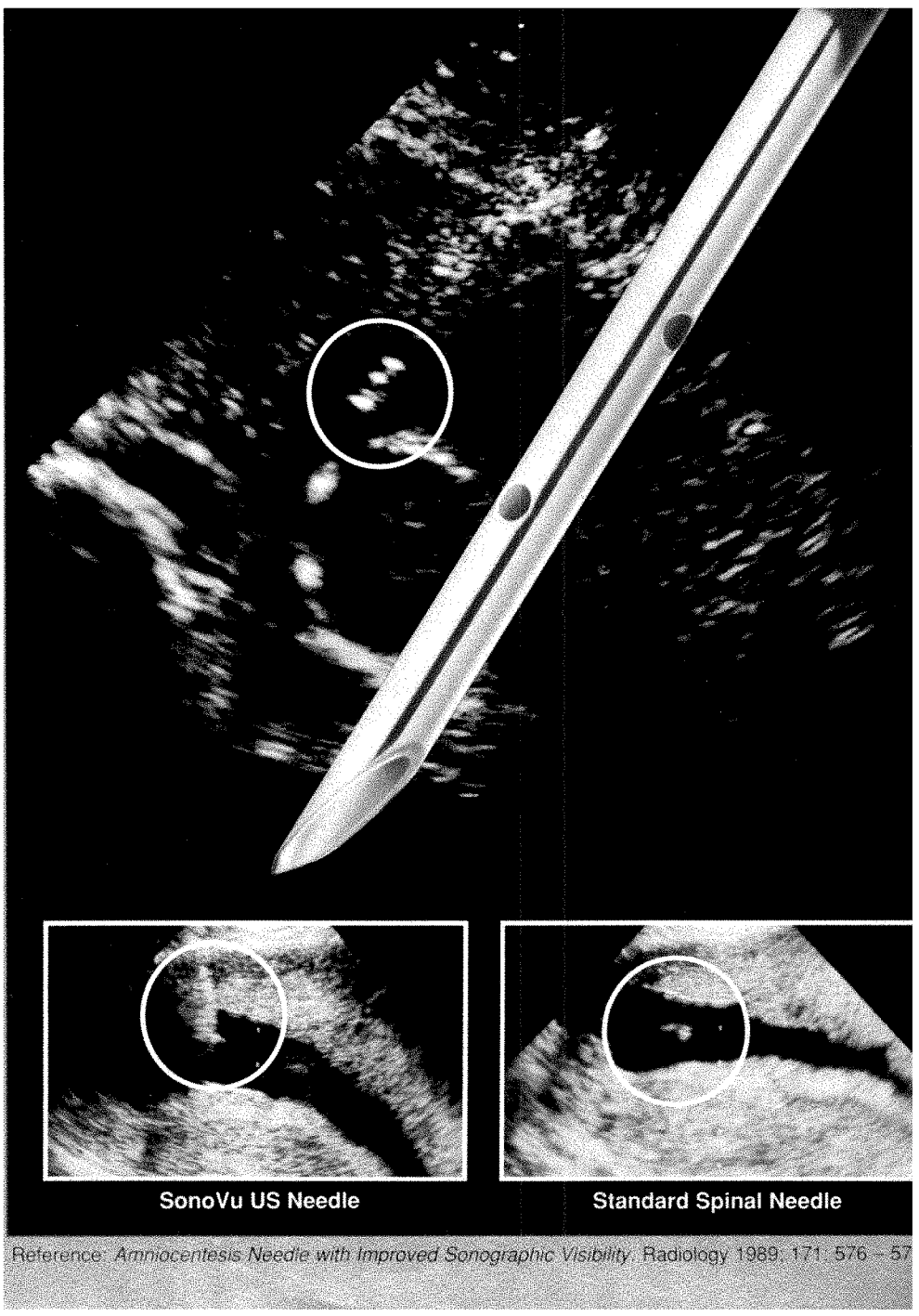
Ultrasonographic evaluation of uteroplacental blood flow patterns abnormally located and adherent placentas

Glenford P. Guy, MD, David B. Peisner, MD, and Ilan E. Timor-Tritsch, MD
New York, New York

Patients with placenta previa and pulsatile placental lacunar flow had a higher risk loss, abnormally adherent placenta, and cesarean hysterectomy.

(Content

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Reference: *Amniocentesis Needle with Improved Sonographic Visibility*, Radiology 1989; 171: 576 - 57

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Gary D. V. Hankins, MD, Curtis L. Lowery, Jr., MD, Richard T. Scott, MD, W. Robert Morrow, MD, K. D. Carey, DVM, PhD, M. Michelle Leland, DVM, and Edward V. Colvin, MD
Lackland Air Force Base and San Antonio, Texas, and Birmingham, Alabama

After oral administration of azidothymidine to pregnant baboons, both azidothymidine and 5'-glucuronide azidothymidine showed a concentration gradient; the level increased from maternal serum to fetal serum to amniotic fluid.

A protocol for managing severe preeclampsia in the second trimester 733
Baha M. Sibai, MD, Sherif Akl, MD, Fiona Fairlie, MD, and Michael Moretti, MD
Memphis, Tennessee

Expectant management with aggressive maternal and fetal monitoring improves perinatal outcome in a select group of patients with severe preeclampsia in the second trimester.

Catastrophic complications of previous cesarean section 738
Cynthia Chazotte, MD, and Wayne R. Cohen, MD
Bronx, New York

The risk of serious morbidity or mortality in this series of 711 pregnancies complicated by previous cesarean section was 2.4%.

Antibiotic therapy in preterm premature rupture of membranes: A randomized, prospective, double-blind trial 743
Matthew M. Johnston, MD, Luis Sanchez-Ramos, MD, Arthur J. Vaughn, MD, Mark W. Todd, PharmD, and Guy I. Benrubi, MD
Jacksonville, Florida

Antibiotic use in preterm premature rupture of the membranes decreases the maternal infection rate, prolongs the delivery latency period, and results in improved neonatal outcome.

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Effect of tocolytic agents on fetal umbilical velocimetry 748
Jeffery W. Wright, MD, Robert M. Patterson, MD, Louis E. Ridgway III, MD, and Michael D. Berkus, MD
San Antonio, Texas

Umbilical artery systolic/diastolic ratios decline in patients treated with terbutaline, but not in those treated with magnesium.

Does the umbilical artery systolic/diastolic ratio reflect flow or acidosis? 751
Joshua A. Copel, MD, Donald Schlafer, DVM, MS, PhD, Richard Wentworth, PhD, Kathy Belanger, PhD, Lois Kreitzer, MS, John C. Hobbins, MD, and Peter W. Nathanielsz, MD, PhD
New Haven, Connecticut, and Ithaca, New York

The placentas of fetal sheep were acutely embolized and it was demonstrated that reductions in flow occurred before changes in the umbilical systolic/diastolic ratio.

Infection and labor. VI. Prevalence, microbiology, and clinical significance of intraamniotic infection in twin gestations with preterm labor 757
Roberto Romero, MD, Fayek Shamma, MD, Cecilia Avila, MD, Carlos Jimenez, MD, Robert Callahan, BS, Jose Nores, MD, Moshe Mazor, MD, Carol A. Brekus, MSN, CNM, and John C. Hobbins, MD
New Haven, Connecticut

Microbial invasion of the amniotic cavity occurred in 10.8% of patients with twin gestations and preterm labor.

Superiority of the four-quadrant sum over the single-deepest-pocket technique in ultrasonographic identification of abnormal amniotic fluid volumes 762
Thomas R. Moore, MD
San Diego, California

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Randomized investigation of magnesium sulfate for prevention of preterm birth 767
Susan M. Cox, MD, M. Lynne Sherman, RN, and Kenneth J. Leveno, MD
Dallas, Texas

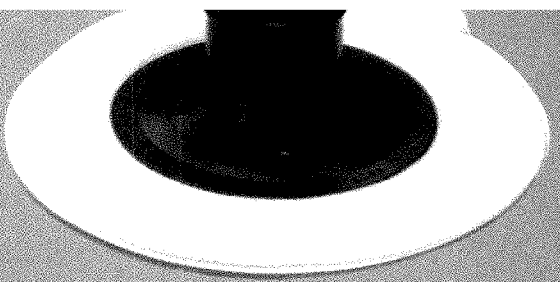
In a randomized controlled study of 156 pregnancies complicated by preterm labor magnesium sulfate was not an effective tocolytic agent.

Fetal gastroschisis and omphalocele: Is cesarean section the best mode of delivery? 773
David F. Lewis, MD, Craig V. Towers, MD, Thomas J. Garite, MD, David N. Jackson, MD, Michael P. Nageotte, MD, and Carol A. Major, MD
Orange, Long Beach, and Pasadena, California

Mode of delivery of infants with abdominal wall defects was analyzed, and no difference in neonatal morbidity or mortality was identified.

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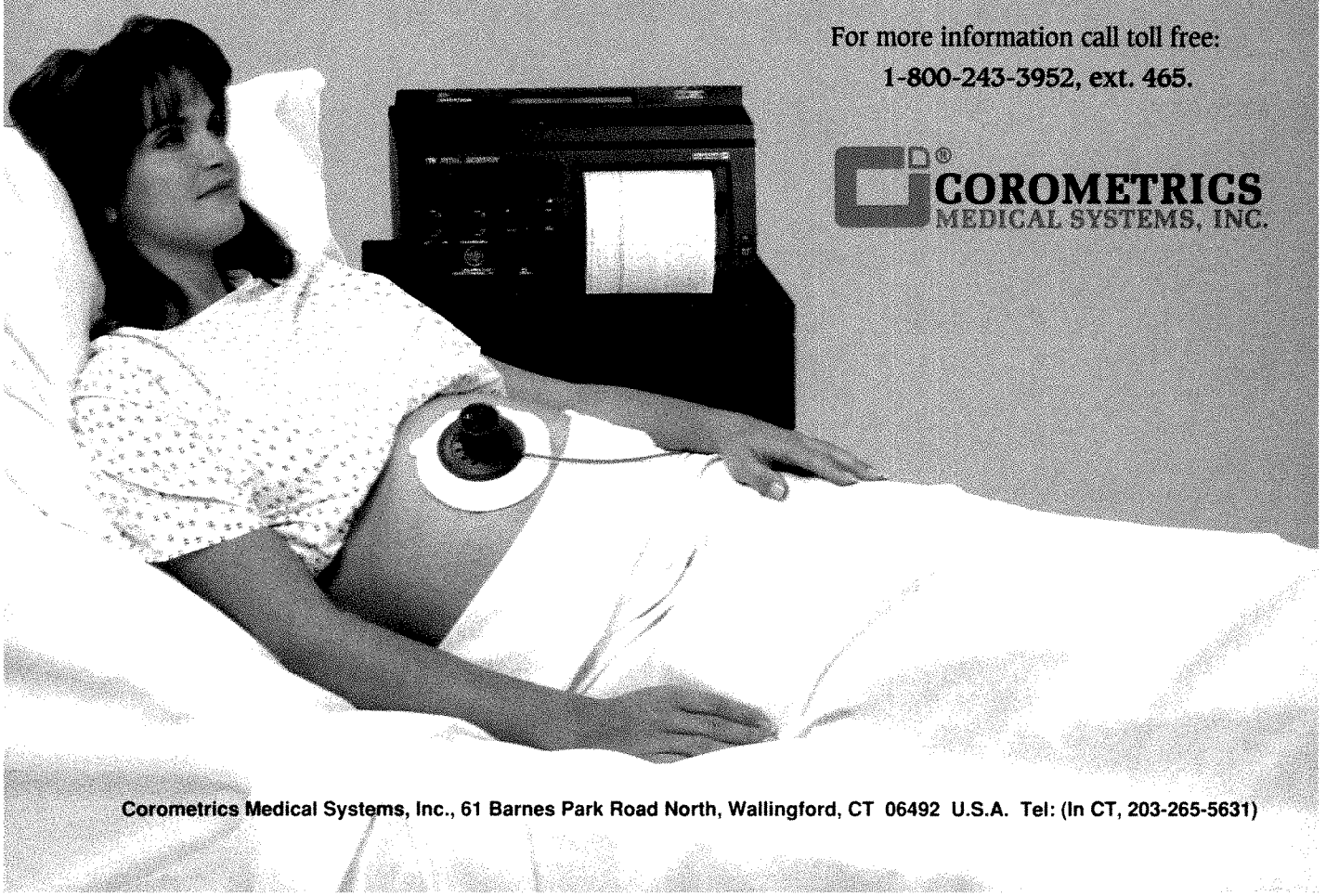


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Kenneth J. Moise, Jr., MD, Giancarlo Mari, MD, David J. Fisher, MD, James C. Huhta, MD, Lorraine E. Cano, RN, and Robert J. Carpenter, Jr., MD
Houston, Texas, and Philadelphia, Pennsylvania

Combined intravascular-intraperitoneal transfusions for treatment of severe red blood cell alloimmunization were associated with a fall in fetal cardiac output and a rise in umbilical venous pressure.

Postinjection kinetics of antepartum Rh immune globulin 784
Frank R. Witter, MD, Rosetta S. Shirey, MS, Suzy L. Nicol, BS, and Paul M. Ness, MD
Baltimore, Maryland

Administration of 300 μg of Rh immune globulin at 28 weeks consistently produces detectable antibodies at 42 days after injection but not at 84 days after injection.

Magnesium sulfate and promethazine do not interact to cause hypotension in gravid ewes 787
Kenneth L. Pollack, MD, David H. Chestnut, MD, Carl P. Weiner, MD, Christine S. Thompson, and Craig S. DeBruyn
Iowa City, Iowa

Magnesium sulfate and promethazine did not interact to cause maternal hypotension in normovolemic gravid ewes.

Uterine hyperstimulation after low-dose prostaglandin E_2 therapy: Tocolytic treatment in 181 cases 794
Christian H. Egarter, MD, Peter W. Husslein, MD, and William F. Rayburn, MD
Vienna, Austria, and Omaha, Nebraska

Uterine hyperstimulation after local prostaglandin E_2 therapy is an uncommon finding and rapidly reversible with β_2-adrenergic therapy.

Prevalence of use of cocaine and other substances in an obstetric population 797
Cristina Matera, MD, Wendy B. Warren, MD, Maureen Moomjy, MD, Daniel J. Fink, MD, and Harold E. Fox, MD
New York, New York

Five hundred nine consecutive urine toxicologic screens in patients admitted to an urban university hospital labor room revealed a 10% prevalence of cocaine use.

A comparison of the effect of epidural, general, and no anesthesia on funic acid-base values by stage of labor and type of delivery 802
Jaye M. Shyken, MD, James S. Smeltzer, MD, L. V. Baxi, MD, Karin J. Blakemore, MD, Steven E. Ambrose, MD, and Roy H. Petrie, MD, ScD
St. Louis, Missouri

Epidural anesthesia offers no clear-cut metabolic advantage to the normal, term fetus undergoing vaginal delivery or cesarean section.

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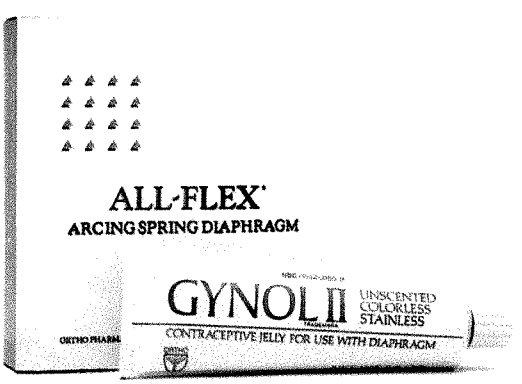
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Effect of uterine contractility and maternal hypotension on prolonged decelerations after bupivacaine epidural anesthesia 808
Ralph M. Steiger, MD, and Michael P. Nageotte, MD
Orange and Long Beach, California

Patients with prolonged decelerations after bupivacaine epidural anesthesia were more likely to have uterine hypertonus and as likely to have maternal hypotension as control subjects.

The effect of amnioinfusion on uterine pressure and activity: A preliminary report 813
Marvin D. Posner, MD, Susan A. Ballagh, MD, and Richard H. Paul, MD
Los Angeles, California

Uterine tone and activity are compared before, during, and after intrapartum transcervical saline solution amnioinfusion, and a case of uterine hypertonus is discussed.

Comparison of umbilical artery pH and 5-minute Apgar score in the low-birth-weight and very-low-birth-weight infant 818
Craig F. Stark, MD, Ronald S. Gibbs, MD, and Walter L. Freedman, MD
Denver, Colorado

In low-birth-weight infants 5-minute Apgar score varies with birth weight, and both umbilical artery pH and Apgar score are influenced by small-for-gestational-age and appropriate-for-gestational-age categorization.

Preterm delivery: A risk factor for retained placenta 823
Roberto Romero, MD, Yu Chiung Hsu, MD, Apostolos P. Athanassiadis, MD, Zion Hagay, MD, Cecilia Avila, MD, Jose Nores, MD, Alistair Roberts, MD, Moshe Mazor, MD, and John C. Hobbins, MD
New Haven, Connecticut

Preterm delivery is a risk factor for retained placenta.

Fetal umbilical artery Doppler response to graded maternal aerobic exercise and subsequent maternal mean arterial blood pressure: Predictive value for pregnancy-induced hypertension 826
R. F. Hume, Jr., MD, MAJ, MC, USA, J. D. Bowie, MD, C. McCoy, MD, P. C. Magarelli, MD, PhD, M. Gall, RN, B. S. Hertzberg, MD, B. A. Carroll, MD, and A. P. Killam, MD
Durham, North Carolina

The fetal umbilical artery Doppler velocimetry response to graded maternal aerobic exercise at 28 weeks' gestation predicts pregnancy-induced hypertension and preeclampsia.

The Shirodkar operation: A reappraisal 830
Faith J. Frieden, MD, Steven A. Ordorica, MD, Iffath A. Hoskins, MD, and Bruce K. Young, MD
New York, New York

A review of 66 consecutive Shirodkar procedures by one surgeon shows this treatment of cervical incompetence to be safe, effective, and compatible with vaginal birth.

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The effect of mode of delivery on the perinatal outcome in fetuses with abdominable wall defects 833
Michael Moretti, MD, Aldo Khoury, MD, Jaime Rodriquez, MD, Thom Lobe, MD, David Shaver, MD, and Baha Sibai, MD
Memphis, Tennessee

A study of 125 infants with abdominal wall defects shows no adverse affects from vaginal delivery on perinatal or long-term outcome.

Perinatal survival with expectant management of midtrimester rupture of membranes 838
Carol A. Major, MD, and John L. Kitzmiller, MD
San Francisco, California

The perinatal survival among 70 patients with midtrimester rupture of membranes managed expectantly was 63%; 68% of survivors had normal neurologic and physical development at 1 year of follow-up.

Double-blind comparison of intravaginal prostaglandin E_2 gel and "chip" for preinduction cervical ripening 845
Carl V. Smith, MD, William F. Rayburn, MD, Robert E. Connor, RPh, Glen R. Fredstrom, RPh, and Corinne B. Phillips, MD
Omaha, Nebraska

A single dose of either prostaglandin E_2 gel or "chip" promoted cervical ripening; a greater risk of uterine hyperstimulation was related to use of the "chip."

Vaginal breech delivery: A five-year prospective evaluation of a protocol using computed tomographic pelvimetry 848
Stefanie Schupp Christian, MD, Kim Brady, MD, John A. Read, MD, and Jerome N Kopelman, MD
Tacoma, Washington

Computed tomographic pelvimetry is an effective tool in the assessment for vaginal delivery of the singleton term frank breech fetus.

The incidence of significant fetomaternal hemorrhage in patients undergoing cesarean section 855
Nathalie Feldman, MD, Amanda Skoll, MD, and Baha Sibai, MD
Memphis, Tennessee

Fetomaternal hemorrhage of >30 ml was detected in 2.5% of 199 patients who had undergone cesarean section for all indications.

Prediction of risk for preterm delivery by ultrasonographic measurement of cervical length 859
H. Frank Andersen, MD, Clark E. Nugent, MD, Suzanne D. Wanty, RN, MSN, and Robert H. Hayashi, MD
Ann Arbor, Michigan

Cervical effacement, measured by endovaginal ultrasonography or manual vaginal examination, was significantly associated with preterm delivery.

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Is indicated or spontaneous preterm delivery more advantageous for the fetus? 868
John Owen, MD, Susan L. Baker, MD, John C. Hauth, MD, Robert L. Goldenberg, MD, Richard O. Davis, MD, and Rachel L. Copper, MSN
Birmingham, Alabama

A case-control study showed no survival advantage in fetuses who underwent indicated preterm delivery.

Evaluation of a risk scoring system as a predictor of preterm birth in an indigent population 873
John Owen, MD, Robert L. Goldenberg, MD, Richard O. Davis, MD, Katharine A. Kirk, PhD, and Rachel L. Copper, MSN
Birmingham, Alabama

The clinical utility of a risk scoring system for the prediction of spontaneous preterm birth in an indigent population is limited.

A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis 879
Louis E. Ridgway III, MD, Kevin Muise, MD, Jeffrey W. Wright, MD, Robert M. Patterson, MD, and Edward R. Newton, MD
San Antonio, Texas

In a randomized study oral magnesium was as effective as terbutaline in the maintenance of tocolysis, with fewer side effects and at a lower cost.

Awaiting cervical change for the diagnosis of preterm labor does not compromise the efficacy of ritodrine tocolysis 882
Gregory O. Utter, MD, Sharon L. Dooley, MD, Ralph K. Tamura, MD, and Michael L. Socol, MD
Chicago, Illinois

Awaiting change in cervical effacement and/or dilation in patients dilated <3 cm on admission does not compromise tocolytic efficacy.

Gram stain results from amniocentesis in patients with preterm premature rupture of membranes—Comparison of maternal and fetal characteristics 887
Tamerou Asrat, MD, Michael P. Nageotte, MD, Thomas J. Garite, MD, Steven E. Gocke, MD, and Wendy Dorchester, MPH
Orange and Long Beach, California

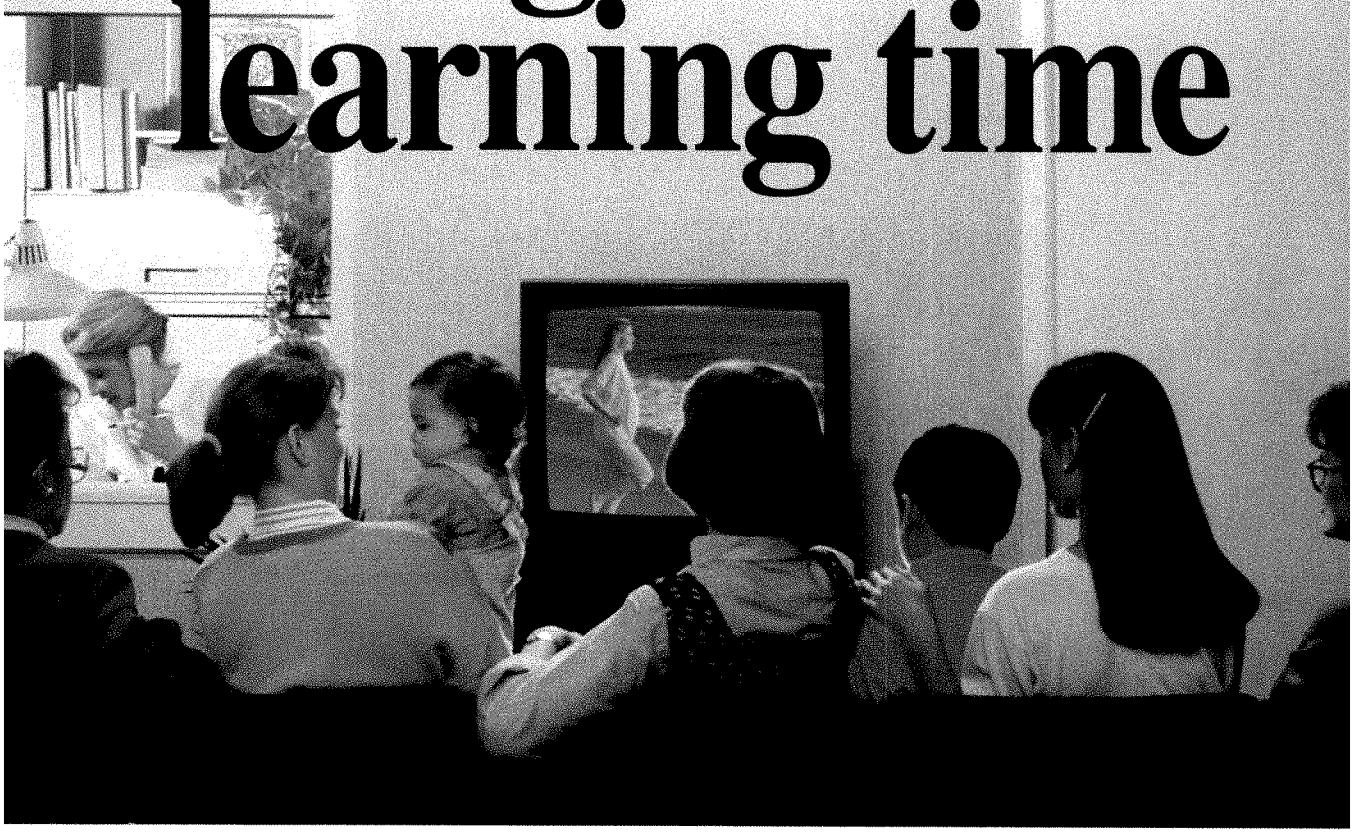
Patients with preterm premature rupture of membranes and positive amniotic fluid Gram stains had higher incidences of elevated fetal heart rate and nonreactive fetal heart rate tracings.

Adjusting the loading dose of magnesium sulfate for tocolysis 889
Jeffrey W. Wright, MD, Louis E. Ridgway III, MD, and Robert M. Patterson, MD
San Antonio, Texas

A method for estimating an adjusted loading dose for magnesium sulfate was established, and this adjusted loading dose was tested in the treatment of preterm labor.

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Infants of diabetic mothers with accelerated fetal growth by ultrasonography: Are they all alike? 893
James D. Keller, MD, Boyd E. Metzger, MD, Sharon L. Dooley, MD, Ralph K. Tamura, MD, Rudy E. Sabbagha, MD, and Norbert Freinkel, MD
Chicago, Illinois

Evaluation of longitudinal ultrasonographic examination and metabolic data in 47 infants of diabetic mothers reveals a growth pattern that raises questions concerning the uniformity of diabetic macrosomia.

Prevalence and etiology of respiratory distress in infants of diabetic mothers: Predictive value of fetal lung maturation tests 898
Siri L. Kjos, MD, Frans J. Walther, MD, PhD, Martin Montoro, MD, Richard H. Paul, MD, Fidelia Diaz, MA, and Mary Stabler, BS
Los Angeles, California

Surfactant-deficient respiratory distress syndrome occurred in 5 of 526 infants of diabetic mothers; the lecithin/sphingomyelin ratio, phosphatidylglycerol, and optical density (650 nm) had 100% sensitivity and 100% negative predictive value.

The relationship between maternal serum and amniotic fluid α-fetoprotein in women undergoing early amniocentesis 903
Cynthia G. Brumfield, MD, Gretchen A. Cloud, MS, Richard O. Davis, MD, Sara C. Finley, MD, John C. Hauth, MD, and Larry Boots, PhD
Birmingham, Alabama

No correlation was found between α-fetoprotein levels in the maternal serum and amniotic fluid in pregnancies undergoing early amniocentesis from 12 to 14 weeks' gestation.

Perinatal outcome of forty-nine pregnancies complicated by acardiac twinning 907
Thomas R. Moore, MD, Scott Gale, MD, and Kurt Benirschke, MD
San Diego, California

Outcome of pregnancy complicated by acardiac twinning was related to the relative size of the acardiac to the normal co-twin.

Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats 912
Timothy W. Harstad, MD, Bertis B. Little, PhD, Roger E. Bawdon, PhD, Kraig Knoll, BS, Daniel Roe, BS, and Larry C. Gilstrap III, MD
Dallas, Texas

In this study we evaluated the embryofetal effects of pentamidine and found an increased early embryo loss but no evidence of congenital anomalies.

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An evaluation of the chorionic villus sampling learning curve 917
Richard K. Silver, MD, Scott N. MacGregor, DO, John S. Sholl, MD, Edward D. Hobart, and Jody K. Waldee, RN
Evanston, Illnois

A low fetal loss rate observed during the initial period of a chorionic villus sampling program may not reflect the acquisition of expertise associated with cumulative experience.

The association of single umbilical artery with cytogenetically abnormal pregnancies 922
Devereux N. Saller, Jr., MD, Carol Lynn Keene, MD, Chen-Chih J. Sun, MD, and Stuart Schwartz, PhD
Baltimore, Maryland

Single umbilical artery is associated with certain karyotypic abnormalities including trisomy 13 and trisomy 18 but not trisomy 21.

Transcervical chorionic villus sampling and amniocentesis: A comparison of reliability, culture findings, and fetal outcome 926
J. E. Ferguson II, MD, Dan J. Vick, BA, Joan S. Hogge, MS, and W. Allen Hogge, MD
Charlottesville, Virginia

Pregnancy loss rates were similar after chorionic villus sampling and amniocentesis, but procedure and culture failures were less likely when amniocentesis was used.

Second-trimester placental biopsy for rapid fetal karyotyping 931
A. D. Cameron, MB, ChB, A. M. Mathers, MB, ChB, S. Wisdom, MB, ChB, J. Johnstone, RGN, J. R. M. MacKenzie, MB, ChB, J. J. Walker, MB, ChB, S. J. Imrie, BSc, G. W. Lowther, BSc, DipRCPath, and J. M. Connor, BSc, MD
Glasgow, Scotland

Second-trimester placental biopsy was found to be a useful procedure for establishing fetal karyotypes in pregnancies at significant risk of chromosomal abnormality.

The association of maternal floor infarction of the placenta with adverse perinatal outcome 935
Robert L. Andres, MD, William Kuyper, BA, Robert Resnik, MD, Kathleen M. Piacquadio, MD, and Kurt Benirschke, MD
San Diego, California

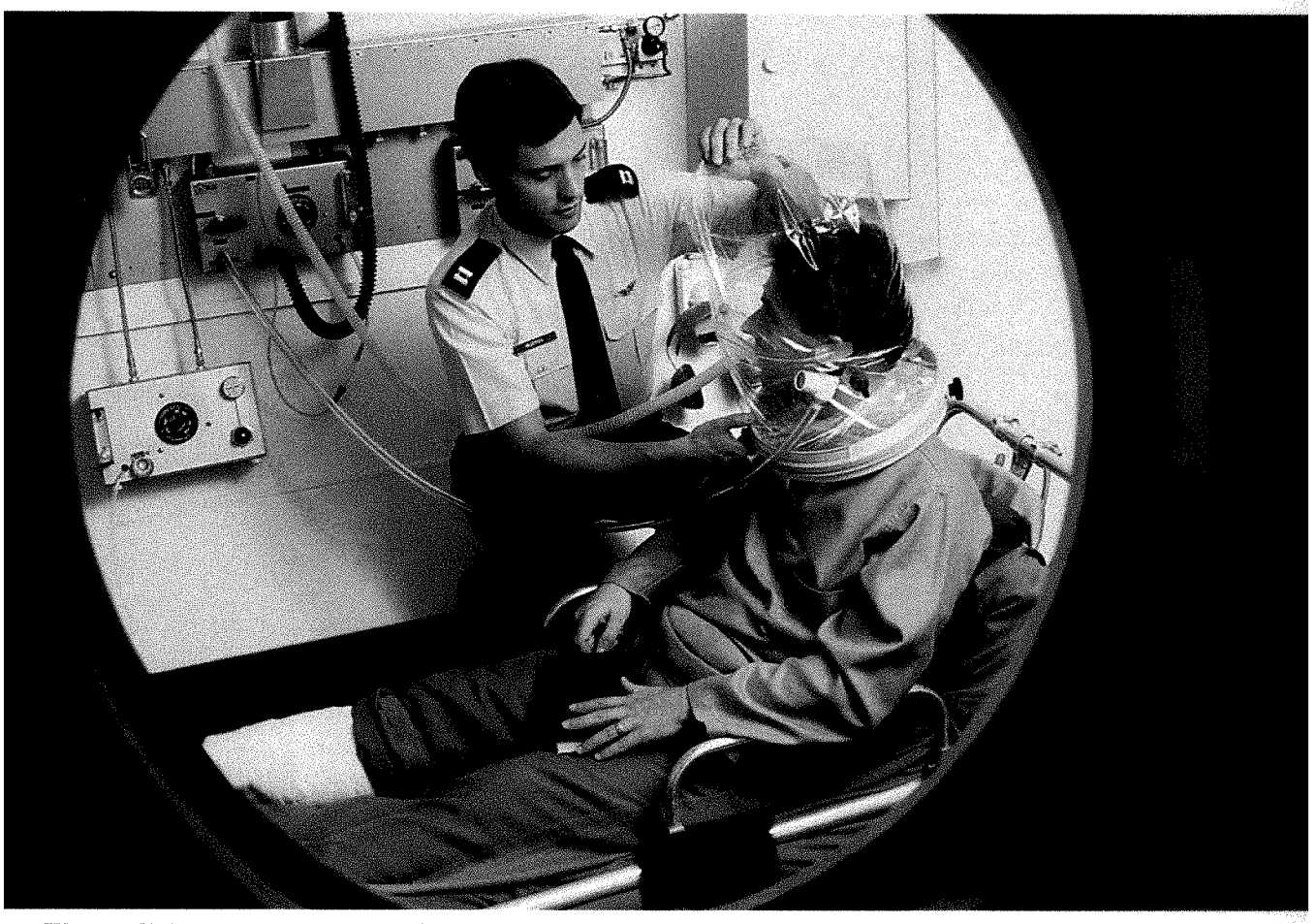
Maternal floor infarction of the placenta is associated with recurrent fetal death, intrauterine growth retardation, and preterm delivery.

Placental transfer of cefazolin and piperacillin in pregnancies remote from term complicated by Rh isoimmunization 938
Charles E. L. Brown, MD, James T. Christmas, MD, and Roger E. Bawdon, PhD
Dallas, Texas

Both cefazolin and piperacillin crossed the placenta promptly in pregnancies remote from term; the presence of hydrops did not impair transfer of cefazolin.

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Ultrastructural aspects of preeclampsia. II. Mitochondrial changes 943
Douglas R. Shanklin, MD, and Baha M. Sibai, MD
Memphis, Tennessee

Direct-vision uterine biopsy specimens obtained at cesarean section or at cesarean section hysterectomy showed extensive myometrial mitochondrial injury in women with preeclampsia but not in normotensive patients; similar mitocondrial injury was found in liver and skin, indicative of a systemic metabolic disorder.

Absence of evidence of pulmonary maturity at amniocentesis in term infants of diabetic mothers 954
Emmanuel O. Ojomo, MD, and Donald R. Coustan, MD
Providence, Rhode Island

Review of 153 charts of diabetic mothers revealed that a significant proportion of women with gestational diabetes (~21%) and overt diabetes (~20%) had absence of phosphatidylglycerol at amniocentesis at term.

Liver histopathologic findings in women with sickle cell disease given prophylactic transfusion during pregnancy 958
Edward Yeomans, MD, Thomas W. Lowe, MD, Edwin H. Eigenbrodt, MD, and F. Gary Cunningham, MD
Dallas, Texas

Forty women with sickle cell disease who underwent prophylactic erythrocyte transfusions during pregnancy had hepatic iron deposition but no evidence of irreversible liver damage.

Comparison of a rapid enzyme-linked immunosorbent assay test and the Gram stain for detection of group B streptococcus in high-risk antepartum patients 965
Craig V. Towers, MD, Thomas J. Garite, MD, Wendy W. Friedman, MT(ASCP), Richard A. Pircon, MD, and Michael P. Nageotte, MD
Long Beach and Irvine, California

An evaluation of a new enzyme-linked immunosorbent assay test combined with the Gram stain for rapid detection of group B streptococcus is presented.

Amniotic fluid glucose concentration: A rapid and simple method for the detection of intraamniotic infection 968
Roberto Romero, MD, Carlos Jimenez, MD, Ajay K. Lohda, MD, Jose Nores, MD, Shuichi Hanaoka, MD, Cecilia Avila, MD, Robert Callahan, BS, Moshe Mazor, MD, John C. Hobbins, MD, and Michael P. Diamond, MD
New Haven, Connecticut

Amniotic fluid glucose determination is a rapid and simple test for the detection of intraamniotic infection.

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False-negative syphilis screening: The prozone phenomenon, nonimmune hydrops, and diagnosis of syphilis during pregnancy 975
Kathleen Berkowitz, MD, Laxmi Baxi, MD, and Harold E. Fox, MD
New York, New York

Patients with false-negative syphilis serology results caused by the prozone phenomenon whose infants had congenital syphilis are described and recommendations for accurate diagnosis made.

Intrapartum hepatitis B screening in a low-risk population 978
J. M. Ernest, MD, Laurence B. Givner, MD, and Robert Pool, MD
Winston-Salem, North Carolina

Intrapartum hepatitis B surface antigen screening in a low-risk population allows timely administration of hepatitis B immune globulin to the newborn.

Risk factors associated with the increasing prevalence of pneumonia during pregnancy 981
K. Berkowitz, MD, and A. LaSala, MD
New York, New York

The rising prevalence and severity of community-acquired antepartum pneumonia are correlated with maternal drug use and human immunodeficiency virus status.

Ultrasonographic fetal weight estimation by an integrated computer-assisted system: Can each laboratory improve its accuracy? 986
Howard O. Thompson, MD, Cynthia Casaceli, BS, and James R. Woods, Jr., MD
Rochester, New York

Estimated fetal weights from 1684 cases were used to evaluate the accuracy, determine institutional weight estimation equation, and establish an optimal examination-to-birth interval.

Ultrasonographic assessment of intestinal damage in fetuses with gastroschisis: Is it of clinical value? 995
Roger R. Lenke, MD, Wayne H. Persutte, BS, RDMS, and Joanne Nemes, RNC
Toledo, Ohio

In those cases of gastroschisis detected prenatally, in utero measurements of fetal bowel seem to be ineffective as indicators for delivery intervention.

Lack of specific placental abnormality associated with cocaine use 998
William M. Gilbert, MD, Christopher M. Lafferty, MD, Kurt Benirschke, MD, and Robert Resnik, MD
San Diego, California

Detailed gross and microscopic examination of placentas from 13 pregnancies complicated by cocaine abuse revealed no specific pathologic abnormalities.

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TRANSACTIONS OF THE FIFTY-SECOND ANNUAL MEETING OF THE SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

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Allan G. W. McLeod, MD
Miami, Florida

Invasive carcinoma of the vulva 1007
Denis Cavanagh, MD, James V. Fiorica, MD, Mitchel S. Hoffman, MD, William S. Roberts, MD, S. C. Peter Bryson, MD, James P. LaPolla, MD, and Desmond P. J. Barton, MD
Tampa, Florida

This is an analysis of 34 years' experience with the surgical management of 415 patients with invasive carcinoma of the vulva, with review of the survival patterns and morbidity.

Bacterial vaginosis and trichomoniasis vaginitis are risk factors for cuff cellulitis after abdominal hysterectomy 1016
David E. Soper, MD, Richard C. Bump, MD, and W. Glenn Hurt, MD
Richmond, Virginia

Patients with bacterial vaginosis and trichomoniasis vaginitis are at increased risk of the development of cuff cellulitis after abdominal hysterectomy.

Cases with ruptured membranes that "reseal" 1024
John W. C. Johnson, MD, Robert S. Egerman, MD, and Jacquelyn Moorhead, MStat
Gainesville, Florida

Patients with preterm prepartal rupture of the membranes that subsequently cease leaking amniotic fluid continue their pregnancies and have improved obstetric outcomes.

The use of serial CA 125 concentrations to monitor endometriosis in infertile women 1032
Donald E. Pittaway, MD, PhD
Winston-Salem, North Carolina

In women with endometriosis and elevated CA 125 concentrations, serial determinations had prognostic value with regard to pregnancy rates and correlated with the clinical course of the disease.

Multiple endocrine adenomatosis type I in pregnancy 1037
Alexander R. Smythe II, MD, Kay F. McFarland, MD, Mohammed Yousufuddin, MD, and William D. Meredith, MD
Columbia, South Carolina

A patient with multiple endocrine adenomatosis type I in pregnancy is presented; diagnosis of insulinoma was confirmed by arteriography and symptoms resolved after delivery and partial pancreatectomy.

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The diagnostic values of concurrent nonstress testing, amniotic fluid measurement, and Doppler velocimetry in screening a general high-risk population 1040

Lawrence D. Devoe, MD, Paula Gardner, RN, Cheryl Dear, RN, and Ramon A. Castillo, MD
Augusta, Georgia

One thousand high-risk obstetric paitents were screened with a combination of nonstress testing, amniotic fluid volume assessment, and Doppler velocimetry; the nonstress test had the highest sensitivity for all risk conditions, whereas test combinations offered the lowest predictive errors for all conditions examined.

Eclampsia. VI. Maternal-perinatal outcome in 254 consecutive cases 1049

Baha M. Sibai, MD
Memphis, Tennessee

There was one maternal death, but morbidity was frequent among 254 patients with eclampsia managed at one perinatal center.

Experience with the EndoPap device for the cytologic detection of uterine cancer and its precursors: A comparison of the EndoPap with fractional curettage or hysterectomy 1055

James P. LaPolla, MD, Santo Nicosia, MD, Charles McCurdy, MD, Curtis Songster, MD, Eugene Ruffolo, MD, William S. Roberts, MD, Mitchel S. Hoffman, MD, James V. Fiorica, MD, and Denis Cavanagh, MD
Tampa and St. Petersburg, Florida

EndoPap uterine cytologic sampling was highly sensitive for the detection of uterine malignancy and atypical endometrial hyperplasia.

Diagnosis and management of prenatally detected myelomeningocele: A preliminary report 1061

William A. Hogge, MD, Jeffrey S. Dungan, MD, Mark P. Brooks, MD, Susan A. Dilks, MD, Patricia L. Abbitt, MD, Siva Thiagarajah, MBBS, and James E. Ferguson, MD
Charlottesville, Virginia

A coordinated management approach to the fetus with myelomeningocele appears to enhance the potential for a favorable outcome.

Outpatient obstetric management of women with type I diabetes 1065

F. John Bourgeois, MD, and Jeanne Duffer, MSN
Charlottesville, Virginia

Perinatal mortality and morbidity were not different in type I diabetic women managed as outpatients when compared with similarly complicated diabetic women managed as inpatients.

Effectiveness of 1% lidocaine dorsal penile nerve block in infant circumcision 1074

Robert M. Arnett, MD, J. Stephen Jones, MD, and Edgar O. Horger III, MD
Charleston, South Carolina

The use of 0.4 ml of 1% lidocaine in dorsal penile nerve blocks decreases stress seen in infant circumcision.

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Reducing cesarean sections at a teaching hospital 1081
Luis Sanchez-Ramos, MD, Andrew M. Kaunitz, MD, Herbert B. Peterson, MD, Beverly Martinez-Schnell, PhD, and Robert J. Thompson, MD
Jacksonville, Florida, and Atlanta, Georgia

At a teaching hospital serving indigent patients, the cesarean section rate was reduced from 28 to 11 per 100 deliveries without compromising neonatal outcome.

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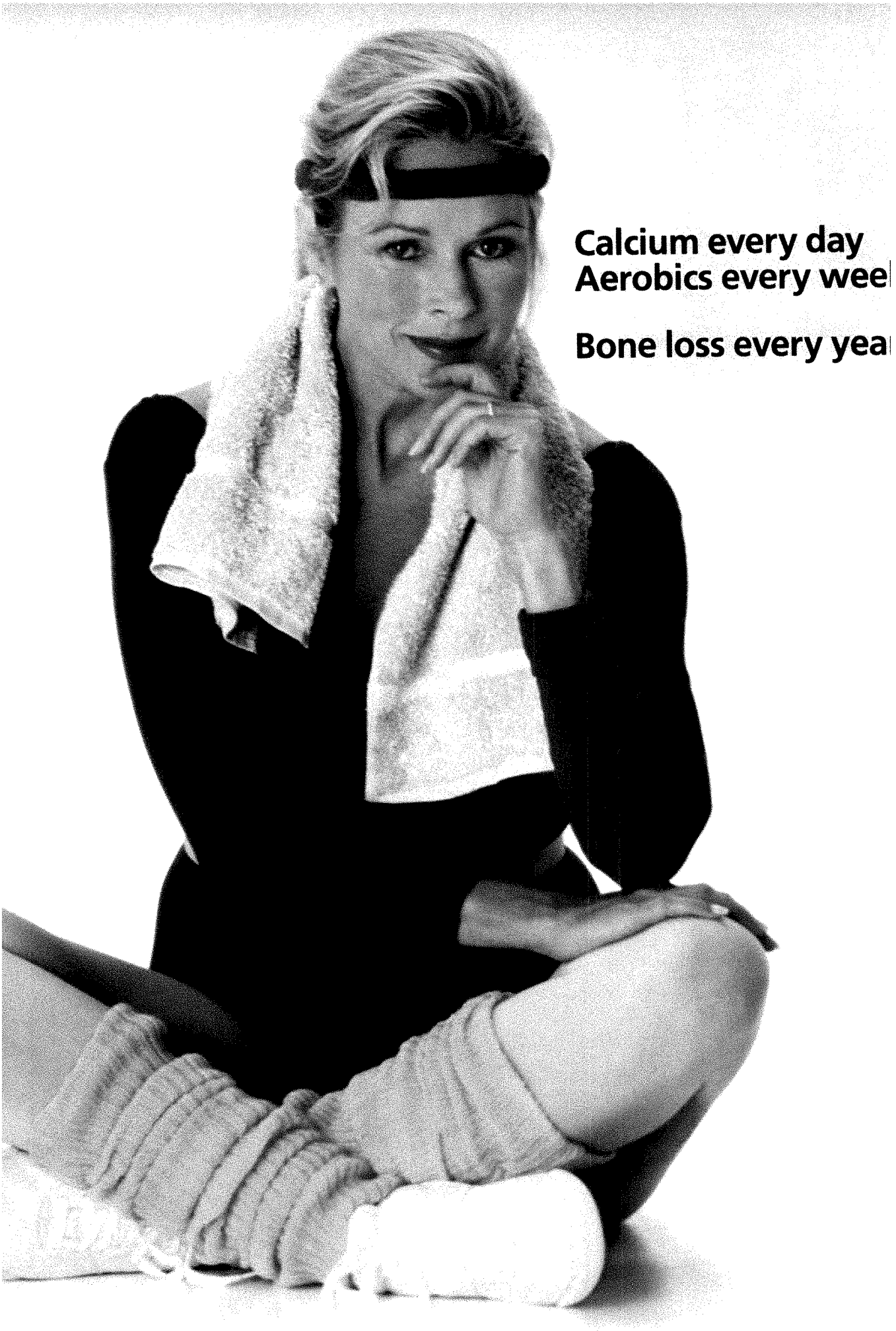
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See important information on adjacent page.

For moderate-to-severe vasomotor symptoms and for osteoporosis

PREMARIN®
(conjugated estrogens tablets)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

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For atrophic vaginitis

PREMARIN®
(conjugated estrogens)

Vaginal Cream
0.625 mg/g



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULARS.)*

PREMARIN® Brand of conjugated estrogens tablets, USP
PREMARIN® Brand of conjugated estrogens Vaginal Cream, in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures including endometrial sampling when indicated should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY. Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the male and female fetus, an increased risk of vaginal adenosis, squamous-cell dysplasia of the uterine cervix, and vaginal cancer in the female later in life. The 1985 DES Task Force concluded that women who used DES during their pregnancies may subsequently experience an increased risk of breast cancer. However, a causal relationship is still unproven, and the observed level of risk is similar to that for a number of other breast cancer risk factors.
There is no indication for estrogen therapy during pregnancy. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion.

DESCRIPTION: PREMARIN (conjugated estrogens, USP) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters. Tablets are available in 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths of conjugated estrogens. Cream is available as 0.625 mg conjugated estrogens per gram.

INDICATIONS AND USAGE: Moderate-to-severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.) Prevention and management of osteoporosis (abnormally low bone mass). Atrophic vaginitis. Atrophic urethritis. Hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

PREMARIN (conjugated estrogens) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected pregnancy (see Boxed Warning). 2. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 3. Known or suspected estrogen-dependent neoplasia. 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. Estrogen replacement therapy has not been reported to increase the risk of thrombophlebitis and/or thromboembolic disease. However, there is insufficient information regarding women who have had previous thromboembolic disease.

PREMARIN Tablets and Vaginal Cream should not be used in patients hypersensitive to their ingredients.

WARNINGS: Some studies suggest a possible increased incidence of breast cancer in women taking higher doses of estrogen for prolonged time periods. The majority of studies have not shown an association with usual estrogen replacement doses. Endometrial cancer risk among estrogen users was about 4-fold or greater than in non-users, and appears dependent on treatment duration and estrogen dose. In patients on combined estrogen-progestin therapy, this risk appears to be decreased. (See PRECAUTIONS below.)

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders.

A 2.5-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens has been reported.

Large doses of estrogen such as those used to treat prostate and breast cancer have been shown to increase the risk of non-fatal myocardial infarction, pulmonary embolism, and thrombophlebitis in men. This cannot necessarily be extrapolated to women. However, to avoid theoretical cardiovascular risk caused by high estrogen doses, the doses for estrogen replacement therapy should not exceed the recommended dose.

Blood pressure should be monitored with estrogen use, especially if high doses are used.

Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: The addition of a progestin for 7 or more days of a cycle of estrogen administration reportedly lowers the incidence of endometrial hyperplasia. Studies of endometrium suggest that 10 to 13 days of progestin are needed to provide maximal endometrial maturation and elimination of hyperplastic changes. Additional risk, such as adverse effects on carbohydrate and lipid metabolism, may be associated with the inclusion of progestin in estrogen replacement regimens. The choice of progestin and dosage may be important in minimizing these adverse effects.

Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one without another physical examination being performed. Conditions influenced by fluid retention, such as asl epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may de manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding mastodynia. Pre-existing uterine leiomyomata may increase in size during estrogen use. Estrogens shou used with care in patients with impaired liver function, renal insufficiency, or metabolic bone diseases assoc with hypercalcemia.

The following drug/laboratory test interactions have been reported, some only with estrogen-proc combinations (oral contraceptives):

1. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinepl induced platelet aggregability.
2. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormon measured by T_4 levels determined by column or by radioimmunoassay. Free T_3 resin uptake is decre reflecting the elevated TBG; free T_4 concentration is unaltered.
3. Impaired glucose tolerance.
4. Reduced response to metyrapone test.
5. Reduced serum folate concentration.

MUTAGENESIS AND CARCINOGENESIS: Long-term, continuous administration of natural and syn estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and

PREGNANCY CATEGORY X: Estrogens should not be used during pregnancy. See **CONTRAINDICATI** and Boxed Warning.

NURSING MOTHERS: As a general principle, the administration of any drug to nursing mothers should be only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy; changes in vaginal ble pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of u fibromyomata, vaginal candidiasis, change in amount of cervical secretion; tenderness or enlargement of br nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice; chloasma or melasma that may persist drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hirsutism; steepening of corneal curvature, intolerance to contact lenses; headache, migraine, dizziness, n depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porp edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea and vomiting.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of conjugated estrogens tablets, USP

1. *Given cyclically for short-term use only.* For treatment of moderate-to-severe vasomotor symptoms, atr vaginitis, or atropnic urethritis associated with the menopause (0.3 mg to 1.25 mg or more daily). The lowest that will control symptoms should be chosen and medication should be discontinued as promptly as pos Administration should be cyclic (eg, three weeks on and one week off). Attempts to discontinue or medication should be made at three- to six-month intervals.
2. *Given cyclically:* Hypoestrogenism. Osteoporosis.

Hypoestrogenism due to: Female hypogonadism—2.5 mg to 7.5 mg daily in divided doses for 20 followed by 10 day rest period. If bleeding does not occur by the end of this period, the same dosage sched repeated. Female castration or primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or down according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effi control.

Osteoporosis—0.625 mg daily. Administration should be cyclic (eg, three weeks on and one week of

PREMARIN® Brand of conjugated estrogens Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinu promptly as possible.

Attempts to discontinue or taper medication should be made at three- to six-month intervals.

Usual dosage range: 2 g to 4 g daily, intravaginally, depending on the severity of the condition.

Patients with an intact uterus who are treated with either PREMARIN Tablets or Vaginal Cream shou monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the ev persistent or recurring abnormal vaginal bleeding.

Revised August 21,

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1. Nilas L, Christiansen C, Rødbro P: Calcium supplementation and postmenopausal bone loss. *Br Med J* 289:1103-1106. **2.** Riggs BL: Research Directions in Osteoporosis. Scientific Workshop, National Institu Health, February 9-11, 1987. **3.** Kiel DP, Felson DT, Anderson JJ, et al: Hip fracture and the use of estroc postmenopausal women. *N Engl J Med* 1987;317:1169-1174. **4.** Christiansen C, Christensen MS, Tran Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. 1981;1:459-461.

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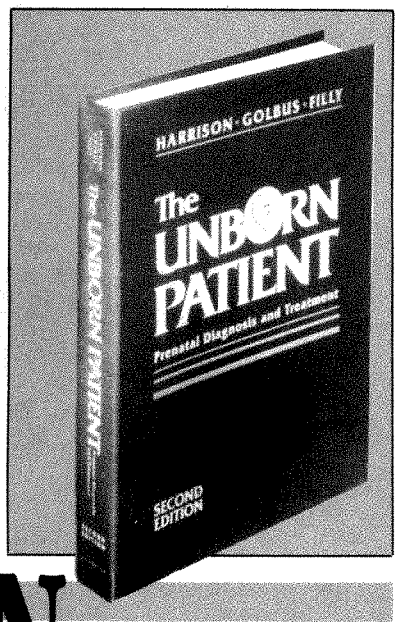
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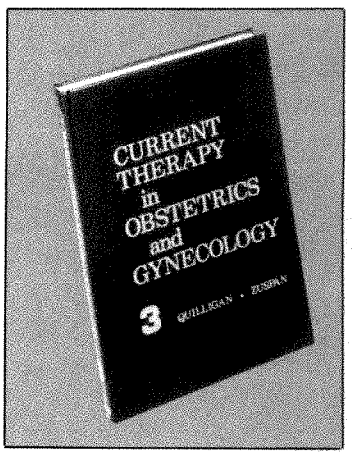
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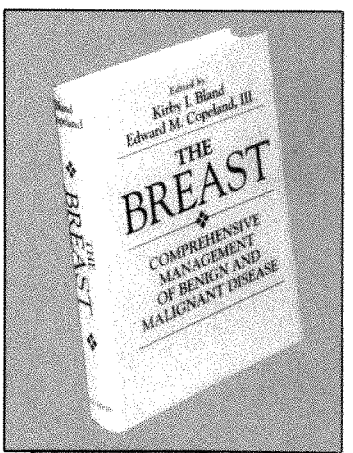
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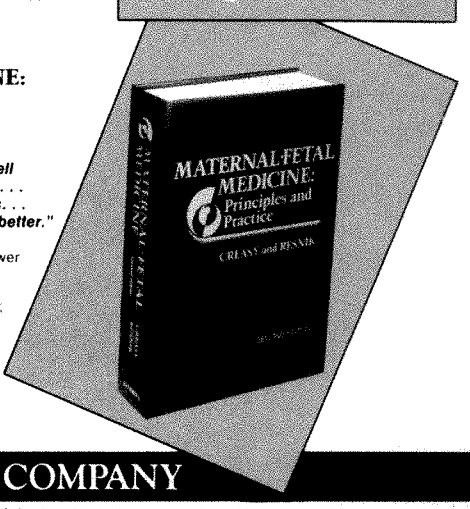


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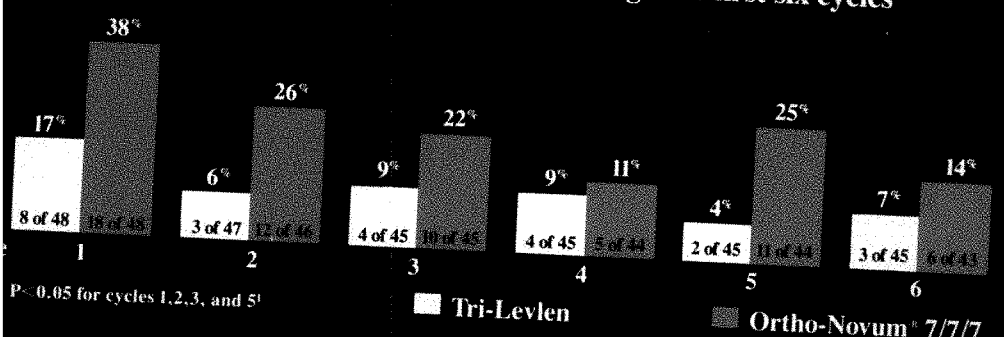
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1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of OCs is well established. Three principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OCs are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION—An increased risk of myocardial infarction associated with the use of OCs has been reported, confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an OC user or not. OCs, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in OCs. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the U.K. estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OCs according to age, smoking habits and duration of use. The overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking and duration of use, nor to compare the effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OCs) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OCs in women over 40 who smoke. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with OCs increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes or history of preeclamptic toxemia and, especially, by cigarette smoking. The physician and the patient should be alert to the earliest manifestations of thrombophlebitis and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four-to-six-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OCs should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Great Britain involving cerebrovascular disease and another study in the United States concerning myocardial infarction suggest that an increased risk of these conditions in users of OCs persists after discontinuation of the OC. In the British study, the risk of cerebrovascular disease remained elevated in former OC users for at least six years after discontinuation. In the U.S. study, an increased risk of myocardial infarction persisted for at least 9 years in women 40- to 49-years-old who had used OCs for five or more years. The findings in both these studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions:* There have been reports of neuro-ocular lesions, such as optic neuritis or retinal thrombosis, associated with the use of OCs. Discontinue OC medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma.* Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina and liver. Certain synthetic progestogens, none currently contained in OCs, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case-control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OCs. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time OCs were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only OCs. Several studies have found no increase in breast cancer in women taking OCs or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with OCs, found an excess risk in the subgroups of OC users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of OCs has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with OCs. Close clinical surveillance of all women taking OCs is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use OCs.

4. *Hepatic Tumors:* Benign hepatic adenomas have been found to be associated with the use of OCs. One study showed that OC formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of OCs. Two studies relate risk with duration of use of OCs, the risk being much greater after 4 or more years of OC use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking OCs. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring and Malignancy in Female Offspring.* The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence at the present time that OCs further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OCs. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including OCs, in pregnancy. One case-control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OCs, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OCs. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OCs is unknown. It is recommended that, for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and further use of OCs should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue OCs with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease:* Studies report an increased risk of surgically confirmed gallbladder disease in users of OCs and estrogens. In one study, an increased risk appeared after 2 years of use and doubled after 4 or 5 years of use. In one of the other studies, an increased risk was apparent between 6 and 12 months of use.

7. *Carbohydrate and Lipid Metabolic Effects.* A decrease in glucose tolerance has been observed in a significant percentage of patients on OCs. For this reason, prediabetic and diabetic patients should be carefully observed while receiving OCs. An increase in triglycerides and total phospholipids has been observed in patients receiving OCs. Three studies have been performed with the Tri-Levlen Tablets (Levonorgestrel and Ethinyl Estradiol Tablets Triphasic Regimen) formulation and no significant alterations in lipid metabolism were noted, with the exception of a slight increase in triglyceride levels in one study. The clinical significance of these findings remains to be defined.

8. *Elevated Blood Pressure.* An increase in blood pressure has been reported in patients receiving OCs. In some women, hypertension may occur within a few months of beginning OC use. In the first year of use, the prevalence of women with hypertension is low in use and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure and in the fifth year of use is two-and-a-half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given OCs. Hypertension that develops as a result of taking OCs usually returns to normal after discontinuing the drug.

9. *Headache:* The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of OCs and evaluation of the cause.

10. *Bleeding Irregularities:* Breakthrough bleeding, spotting and amenorrhea are frequent reasons for patients discontinuing OCs. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of OCs. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive method. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding:* OCs given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in OCs has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of OCs should be deferred until the infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OCs. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, OCs should not be prescribed for longer than 1 year without another physical examination and PAP smear being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking OCs should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. OCs may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving OC therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8. Serum folate levels may be depressed by OC therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OCs, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of OC therapy when relevant specimens are submitted. 10. Certain endocrine and liver-function tests and blood components may be affected by estrogen-containing OCs: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factor VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See "Warnings" section for information on the carcinogenic potential of OCs.

Pregnancy—Pregnancy Category X. See "Contraindications" and "Warnings."

Nursing Mothers—See "Warnings."

Adverse Reactions—An increased risk of the following serious adverse reactions has been associated with the use of OCs (see "Warnings"): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and the use of OCs, although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving OCs and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement and secretion; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of OCs, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, hemolytic uremic syndrome.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OCs by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration—To achieve maximum contraceptive effectiveness, Tri-Levlen Tablets (Levonorgestrel and Ethinyl Estradiol Tablets—Triphasic Regimen) must be taken exactly as directed and at intervals not exceeding 24 hours. (If Tri-Levlen is first taken later than the first day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on it until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.) Any time the patient misses 1 or 2 brown, white or light-yellow tablets, she should also use another method of contraception until she has taken a tablet daily for 7 consecutive days.

For full details on dosage and administration see prescribing information in package insert. 60611-1 5/86

Reference: 1. Data on file, Berlex Laboratories, Inc.

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Metabolism of cocaine by human placentas: Implications for fetal exposure

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To assess placental metabolism of cocaine, placentas were obtained at the time of delivery and the microsomes were extracted by ultracentrifugation within 2 hours. Placental microsomes were cultured with cocaine at physiologic plasma concentrations similar to those of cocaine users (0.75 μg/ml). Two control groups were established. In the first group an anticholinesterase was added to the culture to suppress enzyme activity, and in the second cocaine was cultured alone without placental microsomes to obtain baseline spontaneous conversion of the drug. The results indicate that cocaine is biotransformed by the human placenta, presumably by cholinesterase activity. This suggests that the placenta may provide a moderate degree of protection from cocaine-induced morbidity, such as abruptio placentae and fetal growth retardation, by converting cocaine into less active metabolites. These results also have pharmacogenetic implications because cholinesterase activity varies among individuals. Hence placentas that cannot transform the drug may place the conceptus at greater risk of developmental abnormalities. (AM J OBSTET GYNECOL 1990;163:715-8.)

Key words: Placenta, metabolism, cocaine, microsome, cholinesterase

In this country one in 10 fetuses is exposed to cocaine via maternal abuse.[1] This exposure may result in or contribute to a myriad of medical problems, including increased frequency of congenital anomalies,[2-5] fetal growth retardation,[6, 7] perinatal cerebral hemorrhage or infarction,[8] neonatal withdrawal symptoms,[7, 9] abruptio placentae,[10] premature birth,[5, 7, 11] and stillbirth.[6]

An important defense against physiologically active substances such as cocaine is enzymatic transformation of them in the serum and in select organs. The placenta, which filters the entire maternal-fetal circulation and contains considerable amounts of smooth endoplasmic reticulum, is a strategic metabolic interface between mother and child and may serve a protective role in maternal cocaine abuse. Although researchers have confirmed placental biodegradation of amphetamine, meperidine, paraaminobenzoic acid, and pentobarbital,[12] previous investigation of placental metabolism of cocaine was confounded by use of frozen placental tissue.[13]

The purpose of this study was to assess the ability of the human placenta to transform maternal serum cocaine into its metabolites. This information is essential to better understand the fetal risk of cocaine-induced morbidity and mortality.

Material and methods

A dozen placentas from routine pregnancies were collected at the labor and delivery unit of Parkland

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Memorial Hospital in Dallas from term mothers who had uncomplicated vaginal or cesarean deliveries. The placentas were placed on ice and transported to the laboratory within 30 minutes of delivery.

Placentas of women with clinically recognized infectious disease or a history of drug abuse were excluded from the study. Inquiries into maternal drug use were made throughout the prenatal course and reported in the patient's chart; consistent negative responses by the mother were considered reliable for this study.

The experiment was designed according to a previously published protocol.[12] In the laboratory the placentas were manually compressed and rinsed in a large volume of cold saline solution. Approximately 25 gm of tissue was resected from randomly selected areas of each placenta, and each piece of tissue was rinsed again with cold saline solution. This rendered the tissue essentially free of blood. The tissue was then minced and homogenized with a Tekmar Tissumizer SDT-1810 in two volumes of cold 0.1 M potassium phosphate buffer, pH 7.4.

The resultant 75 ml of homogenate was transported on ice to a Sorvall RCFC centrifuge, divided equally into two tubes, and centrifuged at 9000 *g* for 15 minutes at 4° C. The supernatant resulting from one tube was refrigerated at 4° C for 1 hour. The supernatant from the second tube was subjected to centrifugation at 104,000 *g* for 1 hour at 4° C with a Beckman L8-70M ultracentrifuge. The latter method produced a pellet of concentrated microsomal proteins. The pellet was collected and reconstituted in phosphate buffer.

Assay solutions were prepared by combining 4 ml of enzyme preparation with 0.75 μg/ml cocaine and phosphate buffer, resulting in a final volume of 5 ml. This concentration of cocaine has been documented to be achievable through typical intranasal administration.[14] In accordance with published protocol,[12] the majority of the assay solutions were prepared with the low-speed (9000 *g*) centrifugate; the microsomal fraction produced by ultracentrifugation was verified to be the source of the activity for each placenta.

Two control groups were established. Anticholinesterase (1,5-bis(4-allyldimethylammoniumphenyl)-pentan-3-one dibromide (obtained from Sigma Chemical Co.) was added to a group of assay solutions (3 mg/5 ml) to selectively inhibit placental cholinesterases. In addition, cocaine (0.75 μg/ ml) was added to phosphate buffer in the absence of placental supernatant to establish baseline spontaneous conversion of the drug.

Time elapsed from removal of tissue from circulation (i.e., delivery) to initiation of incubation averaged 3½ hours. Each 5 ml aliquot was incubated at 37° C in a shaking water bath for a total time of 135 minutes, with a 1 ml sample taken at initial composition and then every 45 minutes. These intervals were based on data that the half-life of cocaine in the human is approximately 45 minutes.[14]

At each interval the 1 ml sample was immediately frozen at −70° C. Subsequently the samples were thawed and cocaine and its metabolites were isolated according to an alkaline drug extraction protocol developed in our laboratory. Relative concentrations of cocaine were obtained from the injection of 3 μl of the extract into the capillary column of a Hewlett Packard 5890A gas chromatograph. Our standard curve for determining absolute cocaine concentrations used lidocaine as an internal standard. Lidocaine was a reliable standard; it was not used systemically as part of the anesthetic procedures during cesarean delivery.

Linear regression of six different lidocaine-cocaine concentrations plus a zero point produced a standard curve with an R^2 value of 0.96 ($R = 0.98$). Newman-Keuls multiple comparisons were used to analyze the difference in cocaine concentrations between groups over time. Tests were performed on The University of Texas Southwestern Medical Center's VAX8800 computer with UTSTAT software.

Results

Our results demonstrate a 20% decrease in the concentration of cocaine over the period of the experiment; the majority of the decline occurred in the first 45-minute interval (Fig. 1). This is a statistically significant ($p < 0.01$) decrease as indicated by the fact that the ending point is ≥7 SEs below the starting point (Table I). The spontaneous conversion of cocaine (cocaine alone without microsomes) was minimal over the time periods studied. Similarly, the concentration of cocaine did not decrease with the inhibiting addition of the anticholinesterase; the beginning and ending values vary by <1 SE.

Comment

Cocaine is sympathomimetic; it inhibits the reuptake of norepinephrine at adrenergic nerve endings. Cocaine exerts its maternal-fetal physiologic effects by its action on the uteroplacental vasculature and myometrium. This tonic sympathetic stimulation results in acute maternal hypertension, which may lead to abruptio placentae.[10] β-Agonism of the myometrium results in increased uterine contractility and enhanced risk of premature rupture of membranes and preterm labor.[15] Uteroplacental insufficiency resulting from vasoconstriction of the uterine arteries has been correlated with reduced birthweight (<2500 gm), fetal growth retardation (<10th percentile), and fetal intolerance to labor.[11] Cocaine also may induce embryofetal systemic vasoconstriction, resulting in the documented incidence of cardiovascular,[5] genitourinary,[2, 3] gastrointes-

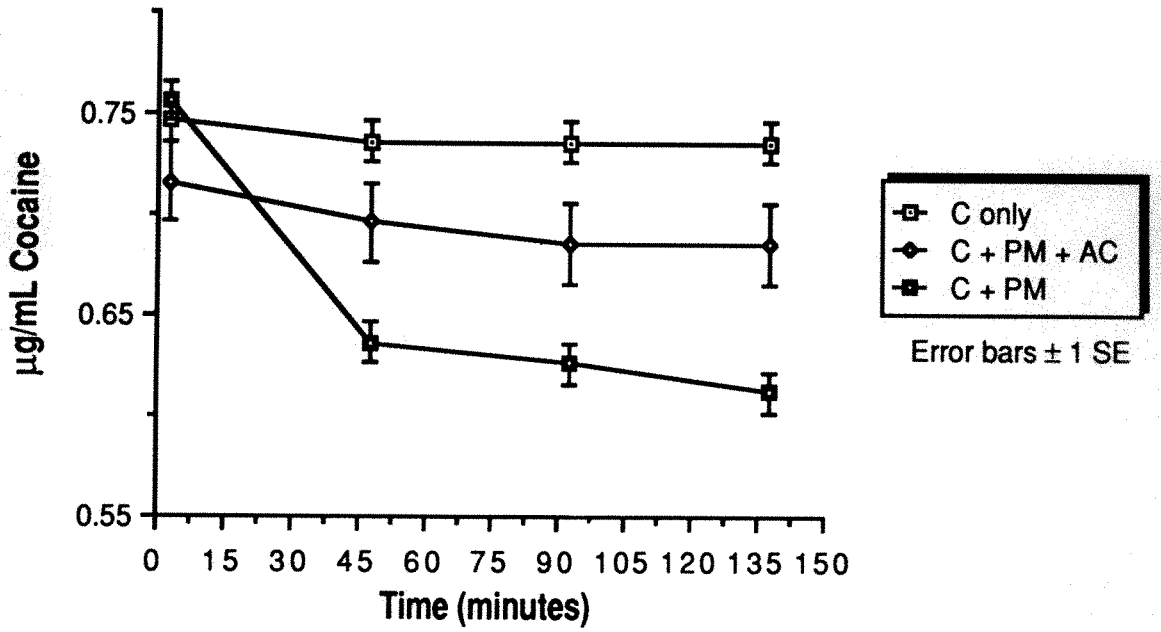


Fig. 1. Change in concentration of cocaine over time in three groups: cocaine alone *(C only)*, cocaine plus placental microsomes plus anticholinesterase *(C + PM + AC)*, and cocaine plus placental microsomes *(C + PM)*.

Table I. Newman-Keuls multiple comparisons analysis of differences in cocaine concentration over time (n = 12 per time period)

Time (min)	Group I. C only*		Group II. C + PM		Group III. C + PM + AC		Group differences†					
							I vs II		I vs III		II vs III	
	Mean	SE	Mean	SE	Mean	SE	Q	p	Q	p	Q	p
0	0.74	0.01	0.75	0.01	0.71	0.02	1.0	NS	3.0	NS	4.0	<0.05
45	0.73	0.01	0.63	0.01	0.69	0.02	7.1	<0.01	2.8	NS	4.2	<0.05
90	0.73	0.01	0.62	0.01	0.68	0.02	7.8	<0.01	3.5	NS	4.2	<0.05
135	0.73	0.01	0.60	0.01	0.68	0.02	9.1	<0.01	3.5	NS	5.7	<0.05

C only, Control group; *C + PM*, cocaine + placental microsomes; *C + PM + AC*, cocaine + placental microsomes + anticholinesterase.

*$n = 4$.

†Newman-Keuls multiple comparisons, Critical value for Q was 3.9 ($p < 0.05$) for II vs III in time 0 and I vs II for times 45 through 135; critical value for Q was 3.2 ($p < 0.05$) for I vs II in time 0 and I vs III for all times, and II vs III for times 45 through 135.

tinal and musculoskeletal anomalies,[4] as well as perinatal cerebrovascular accidents.[8] Finally, cocaine has an anorectic effect,[16] and its use is associated with an increased incidence of sexually transmitted diseases.[17]

In vivo cocaine is transformed into four metabolites: norcocaine, benzoylecgonine, ecgonine methyl ester, and ecgonine. Each is derived from a separate process. Norcocaine arises from the action of an *n*-demethylase present in adult human liver, but this pathway is not significant in human physiology. Benzoylecgonine appears spontaneously; it is not enzyme dependent. Ecgonine methyl ester results from the action of cholinesterases. Ecgonine is the sequela of both benzoylecgonine and ecgonine methyl ester and may arise from enzymatic hydrolysis.[14]

With consideration of these metabolic pathways the 20% decrease in cocaine concentration observed in this study can be attributed to the action of placental cholinesterase for two reasons: Cocaine levels did not decline when enzymatic inhibition was achieved with anticholinesterase and the decrease in cocaine concentration cannot be ascribed to any nonenzymatic reaction (such as that yielding benzoylecgonine) because the group with cocaine without microsomes exhibited no change.

Thus the biotransformation of cocaine by placental

cholinesterases yields metabolites that are more polar and less pharmacologically active than cocaine. Therefore, this conversion may offer a degree of protection against adverse maternal-fetal effects. This enzymatic activity, present in the term placenta, has not been documented in the first-trimester placenta; therefore the role of the early placenta in protection from cocaine-induced congenital anomalies during the critical developmental period remains to be elucidated.

These results also have pharmacogenetic implications because (1) genetic polymorphisms for cholinesterase exist, creating a broad spectrum of enzymatic potential,[18] (2) cholinesterase deficiency or low activity has been associated with enhanced cocaine toxicity in the adult,[19] and (3) the frequency of low cholinesterase activity or inactivity is 1% to 13% in North America, according to ethnic origin.[18] Hence placentas that cannot transform the drug may place the conceptus at greater risk of suffering cocaine-induced morbidity or mortality.

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Survival rates of monoamniotic twins do not decrease after 30 weeks' gestation

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A search of pathology records from the years 1967 to 1988 at Women and Infants' Hospital of Rhode Island (138,232 live births) revealed 24 sets of histologically confirmed monoamniotic twins. All records were available for review. Among the 17 sets of monoamniotic twins that reached 30 weeks' gestation with at least one twin still alive, there were no further fetal deaths. The risks of early delivery in these pregnancies appear to outweigh the risk of fetal death as a result of monoamniotic status alone. These data do not show an advantage to early delivery. (Am J Obstet Gynecol 1990;163:719-22.)

Key words: Monoamniotic twins, life table analysis, mortality

Monoamniotic twinning is a rare event widely recognized to have increased antenatal and perinatal morbidity and mortality.[1-9] The striking increases in morbidity and mortality rates have focused attention on these pregnancies well in excess of their incidence.

Although the exact incidence of monoamniotic twins is difficult to ascertain, the incidence in various studies ranged from 1 : 1650[10] to 1 : 93,734[7] live births. Because of an impression of increasing morbidity and mortality rates in monoamniotic twin pregnancies with advancing gestational age, delivery early in the third trimester has been advocated.[11] As a result of the rarity of monoamniotic twinning, publications in which their outcome is examined have consisted almost exclusively of case reports or collections of case reports, limiting the conclusions that may be drawn concerning optimal management, and in particular, the timing of delivery.

Methods

Prompted by the admission for preterm labor of a woman carrying monoamniotic twins, a thorough search of records at Women and Infants' Hospital of Rhode Island from the years 1967 to 1988 was carried out. Twenty-four sets of histologically confirmed monoamniotic twins were identified, of which all records were available for review. During the 21-year interval there were 138,232 live births at the hospital. Each of the records was searched for selected prenatal and outcome variables. Death of a twin or twins was considered to be a result of monoamniotic status only if intertwined umbilical cords or vascular anastamoses with evidence of twin-to-twin transfusion were described by the delivering obstetrician or pathologist. All intrauterine deaths in this series met these criteria. Life table analysis was used with survival of at least one twin, and then survival of both twins, as the indicators of a favorable outcome to determine the cumulative proportional fetal survival rates of those monoamniotic twins identified and to determine whether and when during the course of the pregnancy these rates stabilized.

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Results

The significant finding was that there were no further fetal deaths after 30 weeks' gestation in our study sample. Of the 24 sets of monoamniotic twins known to be alive before 18 weeks' gestation, 15 sets were alive/alive at 30 weeks, one set was delivered and survived, two sets were alive/dead, and six sets were dead/dead. Of those 17 sets of twins with at least one twin alive at 30 weeks' gestation, all 17 showed no further fetal death up to the time of delivery (Table I). The life table analysis reveals that the cumulative proportional fetal survival rate with double twin survival stabilized at 0.79 at 30 weeks' estimated gestational age. When survival of at least one twin was used as the indicator of a favorable outcome, the cumulative proportional fetal survival rate stabilized at 0.81 at 30 weeks. The cumulative risk trend for survival of at least one twin is represented graphically in Fig. 1.

Perinatal survival of both twins occurred in 46% of cases, and perinatal survival of at least one twin occurred in 63% of cases. The average gestational age at delivery in those cases with double survival was 36.5 weeks (SD, ±3.38; range, 29 to 42 weeks), and in those cases with at least one survivor was 36.3 weeks (SD, ±3.59; range, 29 to 42 weeks). Antenatal diagnosis of

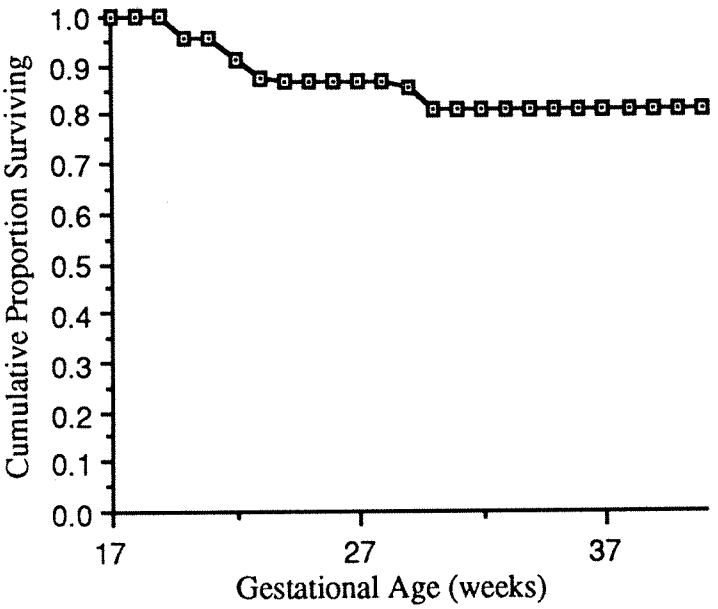


Fig. 1. Cumulative proportional fetal survival rate as function of gestational age with at least one survivor in 24 sets of monoamniotic twins.

Table I. Fetal deaths among monoamniotic twins

<18 weeks	*30 weeks*	*Delivery*
A/A = 24	A/A = 16 A/D = 1 D/D = 6	A/A = 16 A/D = 1 D/D = 6

A/A, Both twins alive; *A/D*, one twin alive and one dead; *D/D*, both twins dead.

monoamniotic twins was made in only 21% of cases, and the diagnosis of twins made in just 29% of cases. Even in the 1980 to 1988 epoch, when the diagnosis of twins was more likely to have been made antenatally, only 44% of cases were identified. Hydramnios was noted as a complicating factor in 25% of cases, and vascular anastamoses between twins were identified in 46% of cases. Vaginal delivery was accomplished in 75% of individual neonates, and in 48% of live-born infants. The sex ratio of our sets of twins was 1.18 (13 sets males, 11 sets females), higher than figures cited.[12] There was no case in which one fetus was delivered vaginally and the other by cesarean section.

The power of life table analysis lies in its ability to determine the extent of ongoing risk to the population under study and to identify the time of minimal risk. Knowing the proportion of the population of interest that survives each given interval, a cumulative proportional fetal survival rate can be calculated as the product of the proportions surviving each interval up to the time of interest. If we are considering delivering a pregnancy early to avoid fetal death, then we need to examine the consequences of that decision. Goldenberg et al.[13] identified week-specific cumulative and incremental survival rates of singleton neonates as a function of gestational age. One minus the week-specific neonatal survival rate yields a week-specific neonatal death rate, and this number can be compared with week-specific fetal death rates attributed to monoamniotic status to arrive at decisions concerning timing of delivery. The probability of two independent events occurring in association is the product of the individual probabilities of those two events. If we assume that the neonatal deaths of both monoamniotic twins (if delivered) are independent events, the week-specific neonatal death rates are the square of the week-specific neonatal death rates for singleton pregnancies as determined by Goldenberg et al.[13] These squared death rate data are presented graphically in Fig. 2. Recall that when in utero survival of at least one twin in each set is used as the marker of a favorable outcome, the cumulative proportional fetal survival rate stabilized at 0.81 at 30 weeks' gestation. This means that a set of monoamniotic twins identified at <18 weeks' gestation with both twins alive can be given an 81% chance of survival of at least one twin to 30 weeks. Conversely, there is a 19% cumulative proportional death rate. This death rate is greatest early in that 18-week to 30-week gestational age interval, and decreases as survival of one or both twins is documented closer and closer to 30 weeks. This decrease in the cumulative proportional fetal death rate is presented in Fig. 3 along with the curve generated from the squared week-specific neonatal death rates derived from the data of Goldenberg et al.[13] At no time does the week-specific fetal death rate because of monoamnionicity alone exceed the week-specific neonatal death rate because of prematurity. It appears from this data set that the risk of fetal death as a result of mono-

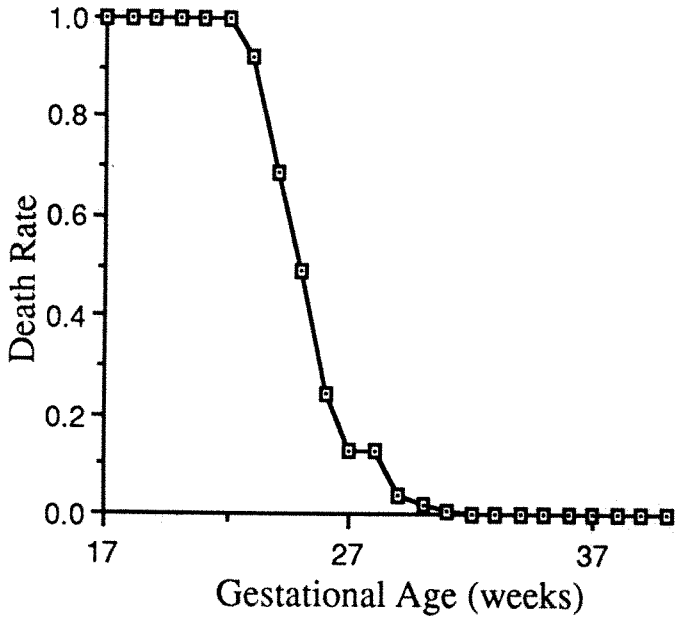


Fig. 2. Neonatal death rates in monoamniotic twins as function of gestational age, assuming that individual deaths are independent events. Data derived from Goldenberg et al. 1984.[13] See Results section for explanation.

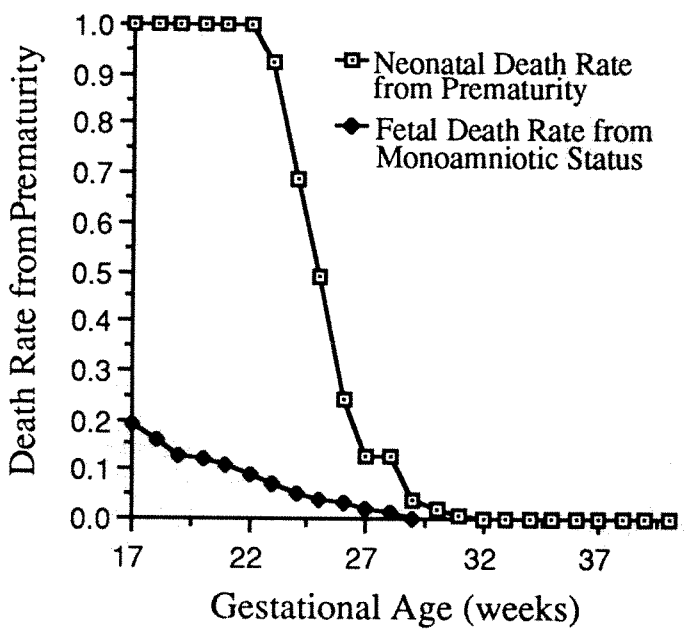


Fig. 3. Week-specific death rates from prematurity and from monoamniotic status alone. Neonatal death rates are derived from data in Goldenberg et al. 1984.[13] Fetal death rates as a result of monoamnionicity are derived from life table analysis as explained in text.

amnionicity is counter-balanced by the improvement in neonatal survival as pregnancy progresses.

Comment

Twins have higher morbidity and mortality rates than do singleton pregnancies,[14-17] and in monoamniotic twins in particular these measures are even higher.[1-10] The particularly high morbidity and mortality rates seen in monoamniotic twins have been attributed to premature delivery, vascular anastamoses between the twins, congenital anomalies, and to intertwining and knotting of the umbilical cords,[1-10] with cord accidents apparently contributing the largest portion. Quigley[1] reported a mortality rate of 68% in monoamniotic twins, and stated that double survival of monoamniotic twins was a rare event. He attributed the

very high mortality rate to intertwining and knotting of the umbilical cords. Twenty-four years later, Salerno[5] reported a double survival rate of 63%, and found that the high mortality rate was primarily a result of cord entanglements and prematurity. The 46% double perinatal survival rate found among our cases agrees well with the 46% survival rate determined by Raphael[8] from a literature review for the time period 1935 to 1961, encompassing 74 sets of monoamniotic twins.

On the basis of small data sets, some authors have advocated delivery of monoamniotic twin pregnancies immediately on demonstration of fetal pulmonic maturity, whenever in the pregnancy that may occur,[2] whereas others have recommended delivery at or about 32 weeks' gestation because of what was thought to be increasing risk as the monoamniotic pregnancy progressed.[11] However, not all authors have agreed with the idea that risks to monoamniotic fetuses necessarily increase as gestational age advances past the early third trimester.[18] These opinions have been expressed with relatively little objective data for support. Whereas our sample size of 24 may appear to be a relatively small number on which to base decisions concerning timing of delivery, no larger population-based data sets are currently available. Our incidence of 1 in 5760 live births agrees well with figures quoted in the literature and suggests that ours is a complete sample.

Our analysis and conclusions may be criticized on the basis of two arguments. The first is the arbitrary decision to use the survival of at least one twin as the marker of a favorable outcome in these pregnancies. When double survival is used as the favorable event marker, the cumulative proportional fetal survival rate is 0.79 at 30 weeks' gestation, only slightly lower than if survival of at least one twin is used. The use of 0.79 as the cumulative proportional fetal survival rate generates cumulative proportional fetal death rates that are slightly higher than those derived above, but they never exceed the week-specific death rate as a result of prematurity alone.

The second argument is with the assumption that the neonatal deaths of a set of monoamniotic twins are independent events. The increased risk of death to the surviving twin in a set of monoamniotic twins with single fetal death is well recognized and is reinforced by our finding that in the eight sets of our twins that had some fetal mortality, it was double mortality in six sets. If we assume that the neonatal deaths of both monoamniotic twins (if delivered) are dependent events, the week-specific neonatal death rate is the sum of the individual week-specific death rates for each of the two twins. This would serve to increase the separation between the week-specific death rate as a result of prematurity and the week-specific death rate as a result of monoamnionicity. Again, we arrive at the same conclusion.

Our data do not reveal an advantage to delivery of monoamniotic twin pregnancies at 32 weeks' gestation. Whereas our sample size of 24 cannot eliminate the possibility of fetal death after 30 weeks' gestation in monoamniotic twin pregnancies, it suggests that these events will be infrequent. Whether demonstration of fetal pulmonic maturity will be an important factor in determining the timing of delivery in these pregnancies remains to be elucidated.

We gratefully acknowledge the assistance of Donald Singer, MD, in obtaining pathology reports on the pregnancies reported here.

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Ultrasonographic evaluation of uteroplacental blood flow patterns of abnormally located and adherent placentas

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Transvaginal ultrasonography was used to evaluate antepartum bleeding in a group of 76 patients at varying gestational ages with suspected placenta previa. The clinical outcome of 16 patients with persistent placenta previa was documented. Nine of the 16 patients had placental lacunar blood flow. Two of the nine patients were lost to follow-up. At cesarean section the seven patients with lacunar flow had a higher incidence of blood loss, transfusion requirements, abnormally implanted placenta, and cesarean hysterectomy than the six patients in whom no lacunar flow patterns were seen ($p = 0.002$). The finding of these flow patterns with abnormally located placentas suggests the anticipation of significant blood loss and probable extension of operative procedures to stop the blood loss. (AM J OBSTET GYNECOL 1990;163:723-7.)

Key words: Placenta previa, placenta accreta, pregnancy, transvaginal ultrasonography, placental blood flow, cesarean hysterectomy

The safe use of transvaginal ultrasonography in patients suspected of placenta previa has been reported.[1, 2] Vaginal transducers enabled accurate imaging of the relationship between the placenta and the internal cervical os. Visual observation of blood flow within the placenta and the related cervical and pelvic blood vessels were also possible. The presence of unusually intense and pulsatile blood flow patterns within several sonolucent structures that appeared to be placental lakes drew our attention to these patients. The purpose of this article is to describe the outcomes in patients with placenta previa and lacunar blood flow.

Material and methods

Seventy-six women with antepartum bleeding and suspected placenta previa were evaluated. A 6.5 MHz mechanical sector scanner (Elscint Ltd., Haifa) at varying frame rates was used. The ultrasonographic texture of these placentas was documented. If lacunar flow was seen within the placenta near or overlapping the internal os the scanning rate was increased for better imaging and a videotape recording of the examination was made. Five of eight patients with lacunar flow were identified both retrospectively by reviewing videotapes and then collecting clinical data. Three of the eight cases were followed up prospectively.

To be confirmed as a lacunar flow pattern, the following placental characteristics were required: thickness > 1 cm with multiple sonolucencies (blood lakes), lakes occupying almost the entire thickness of the placenta from the basal plate to the chorionic plate, and visibility of blood flow (pulsatile and laminar) within these lacunae at high scanning frame rates. The borders between the placental and the myometrial or cervical tissues may not be distinguishable. Dilated vascular structures with pulsatile flow may also be visualized within the nonplacental tissue.

The following clinical outcome data were reviewed retrospectively: previous cesarean section, previous placenta previa, mode of delivery, amount of described blood loss, amount of blood replacement, additional operative procedures (ligation of vessels, hysterectomy), and the histologic feature of the placenta and uterus. Statistical analysis was done with Fisher's exact test. The comparison groups used in both p value calculations were patients with or without lacunar blood flow necessitating cesarean hysterectomy (7/14) or cesarean section (7/13). All of the patients' physicians were aware of the diagnosis of abnormally located placenta, if present, and the lacunar flow pattern. However, the clinical significance of the flow pattern was not yet clear during the early part of the series.

Criteria used for the termination of growth retardation were limited to the postpartum definition of Battaglia and Lubchenco.[3] This identified infants <10th percentile of birth weight for given gestational age (< 2500 gm at term).

Results

There was no increased bleeding in the patients examined after transvaginal ultrasonography. At the initial examination no placenta previa was detected in 13

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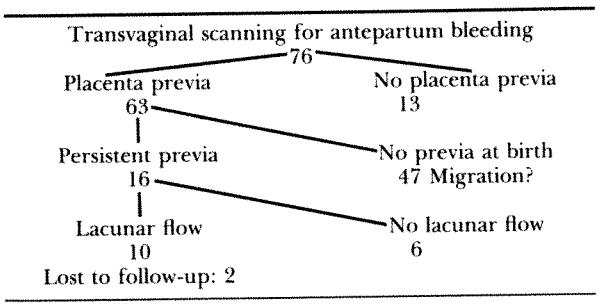


Fig. 1. Patient distribution.

of the 76 patients. Of the remaining 62 patients 16 showed persistent placenta previa. Forty-seven had no placenta previa on subsequent scanning or had vaginal deliveries (Fig. 1). Ten of the 16 patients with persistent placenta previa had lacunar flow patterns. Two of these 10 were lost to follow-up. Seven had homogeneous placentas without the lacunar flow pattern.

The transvaginal ultrasonographic image of a typical patient with a normal homogeneous placenta and a superimposed drawing for orientation is shown in Fig. 2. A typical lacunar structure within an abnormal placenta is shown in Fig. 3.

The outcomes of the eight patients with lacunar flow in the placenta are shown in Table I. Two of the patients with lacunar flow had clinically determined placenta accreta. Patient No. 4 underwent a second laparotomy hours after the cesarean section to control the persistent bleeding. However, a cesarean hysterectomy finally was necessary. Patient No. 2 had a previous placenta previa and six previous cesarean sections. The remaining cases had microscopically determined abnormally implanted placentas. Patient No. 8 refused any further blood transfusion beyond two units against medical advice.

The six patients without flow patterns and homogeneous-appearing persistent placenta previa had cesarean deliveries. None had placenta accreta or a hemorrhagic course necessitating arterial ligation or cesarean hysterectomy.

There were no neonatal or maternal mortalities. The morbidity in all cases emanated from blood loss, operative time, and the impact of transfusion. Patient No. 2 also had disseminated intravascular coagulation. There were two multiple gestations among the patients without lacunar blood flow, and these necessitated preterm deliveries. A total of six preterm deliveries occurred (three from the group with nonflow pattern and three from the lacunar flow group). In cases of term deliveries (> 37 weeks) there were no infants with birth weights < 10th percentile for given gestational age. The average birth weight for the term lacunar flow group (four patients) was 3115 gm (range, 2120 to 3735 gm) and for the term nonlacunar flow group (three patients) 3156 gm (range, 2810 to 3350 gm).

There was a significant risk of hemorrhagic complication necessitating termination by cesarean hysterectomy among the patients with lacunar flow patterns. When compared with blood loss in patients with lacunar flow, the mean estimated blood loss among the patients with nonlacunar blood flow was 967 ml (range, 700 to 1500 ml). The mean estimated blood loss among the patients with lacunar flow was 2900 ml (range, 1000 to 4000 ml). Patients with lacunar flow also had an increased risk of abnormally implanted placenta when compared with patients without lacunar blood flow ($p = 0.002$).

Comment

Transvaginal ultrasonography is highly suited for evaluation of placenta previa because of the direct visualization of the critical tissue areas that the probe provides. In the cases of abnormally implanted placentas, the cervix and the lower uterine segment can be accurately evaluated. The lacunar pattern described here was associated with a high operative risk for increased bleeding in six of the seven patients. This consistency prompted us to study the underlying pathology.

The microhemodynamics of blood flow in the intervillous space is of interest because of the flow patterns we observed. The understanding of the development of normal uteroplacental circulation, and the interaction of the invading trophoblast has come from many sources. Questions remain with regard to the earliest contact of maternal blood with the intervillous spaces.[4] However, the dynamics of uteroplacental blood flow has been demonstrated in primates by Ramsey and Donner[5] with subsequent extrapolations to human placentas. Extravillous trophoblast first migrate from the cytotrophoblastic shell[6] and subsequently from the anchoring villi[7] to penetrate the decidua. The trophoblasts then travel to the inner layer of the myometrium to a depth of a few millimeters.[8, 9] This interstitial migration is thought to prepare the spiral arteries for conversion by the endovascular migratory trophoblast to physiologic (dilated) conduits.[10] This endovascular cytotrophoblastic migration becomes part of the spiral arterial wall to produce the physiologic conversion (dilatation) of these arteries alone.[11] The conversion results in increased volume of blood to the intervillous space and a reduced pulse pressure.[12] Ramsey's classic model of "no preformed channels," and "reduced pulse pressure" were not patterns seen in these placentae. Poiseuillian perfusion, and not the Darcian model of percolation advanced by Schmid-Schonbeim,[13] was seen in these lacunar regions. We observed a pulsatile type of perfusion and turbulent flow in areas where the placenta appeared to have lost parenchyma. The sonolucencies in these areas imparted a "Swiss cheese" pattern

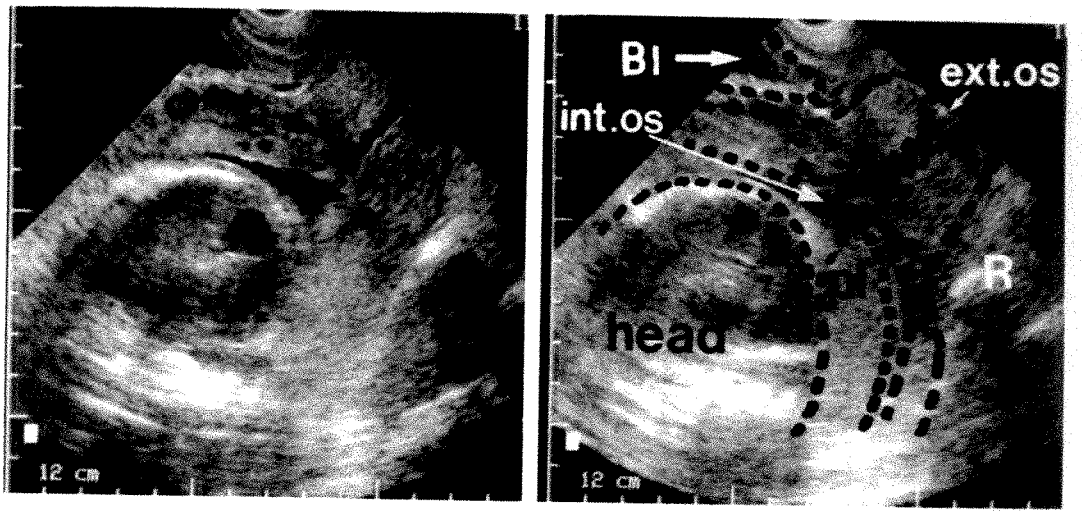


Fig. 2. Transvaginal ultrasonographic sagittal view of relationship between view of uterus, cervix, and normal homogeneous placenta. *Bl* Urinary bladder; *Pl* homogeneous placenta; *R* rectum.

Table I. Case analysis of patients with lacunar blood flow

Case No.	*Gravidity*	*Parity*	*Prior cesarean section*	*Estimated blood loss (ml)*	*Transfusion (units)*	*Cesarean hysterectomy*	*Pathology*
1	5	3	3 LF	4000 ml	5	Yes	Accreta
2	10	9	6 LF	3500ml	14	Yes	Accreta*
3	5	2	None	1000 ml	None	No	Normal
4	7	3	3 LF	3500 ml	7	Yes	Accreta*
5	3	1	1 LF	4000 ml	12	Yes	Accreta
6	7	2	1 LF	1200 ml	4	Yes	Accreta
7	6	2	None	3000 ml	10	Yes	Increta
8	4	3	1 LF	3000 ml	2†	Yes	Accreta

LF, Low flap.
*Clinical diagnosis only.
†Refused further transfusion.

of dilated lacunae to the normally homogeneous placenta. If percolation of maternal blood among the villi is to enhance gas exchange (respiration),[13] then these areas with loss of villi and perfusion flow may have less adequate function. They are virtual respirational dead spaces and act only as conduits. The high hemorrhagic potential given the blood flow observed within them can be visualized. However, it is of interest that growth retardation was not seen in these fetuses.

A strong association between the abnormally adherent placenta and the lacunar flow was found. The histopathogenesis of abnormally adherent placenta results from the reduction of decidua in the placental bed and the trophoblastic invasion of the myometrium.[14, 15] There is an increased incidence of abnormally adherent placentas in the lower uterine and cervical canal where poor decidual reaction occurs.[16] The histopathologic role of previous cesarean section is less clear but its persistent association with abnormally adherent placentas is well documented.[15-19] All these risk factors were found in our patients. Khong and Robertson[20] reviewed 20 cases of placenta accreta to assess the histopathologic correlates of trophoblastic migration and the development of vasculature in these specimens. The most unusual finding was that the physiologic vessel dilation that normally is limited to the spiral arteries was also seen in the higher pressure, larger arteries of the radial, arcuate, and parametrial systems. Many spiral arteries also were found to lack physiologic vessel dilation. Khong and Robertson hypothesized that this pathologic recruitment of the arterial system was to compensate for the frequent findings of inadequate uteroplacental circulation, especially in placenta "previa creta" specimens. The spiral arteries normally conduct blood to the intervillous space under low pressure. The impact on the placental parenchyma of this compensatory neovascularization is unknown. Observations suggest that the blood flow is transmitted from arteries of greater pulse pressure; the impact of this flow will be the focus of our future reports. Our current findings of wide channels, with perfusion flow and pulsatile activity within the placental parenchyma, appear to contradict

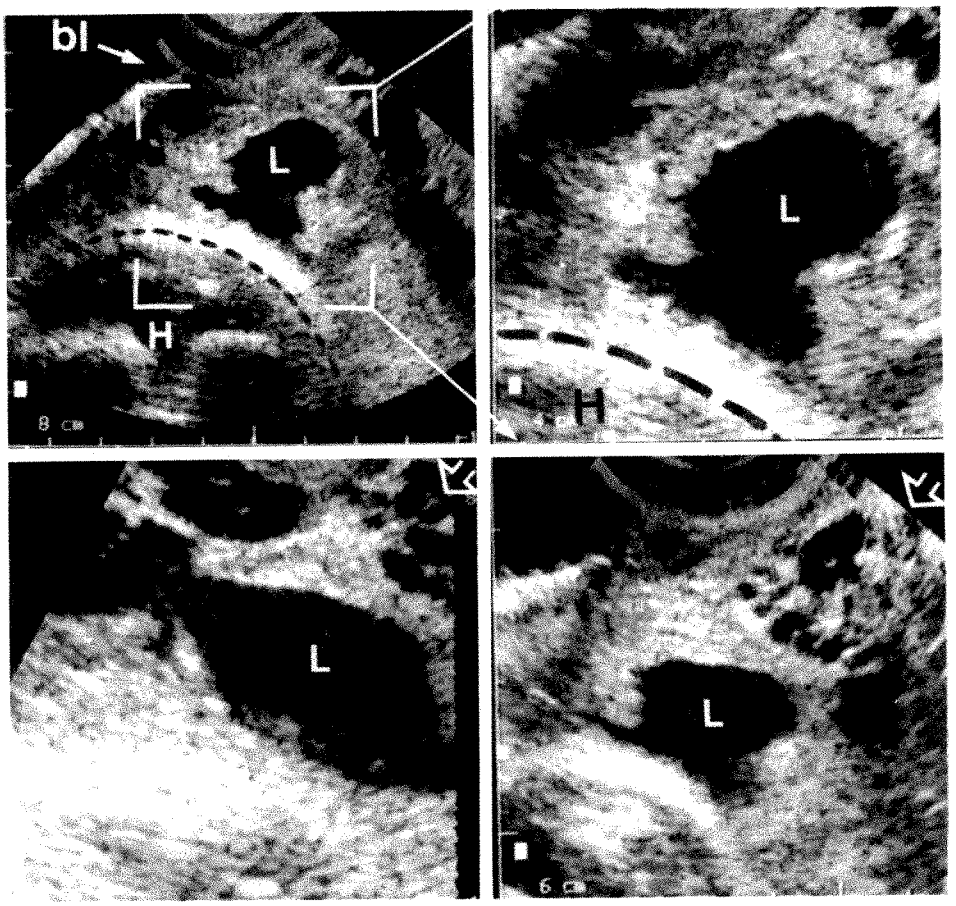


Fig. 3. Transvaginal ultrasonographic sagittal views demonstrate typical "Swiss cheese" pattern of lucencies in abnormally adherent placenta with lacunar flow. *Bl*, Bladder; *L*, lacunae; *H*, head; external os, open arrows.

previously published models pertinent to the microhemodynamics of the intervillous space.

Our observations suggest transmission of high pulse-pressure blood flow from the deep arterial system. The imaged channels and lakes may represent areas of villous attenuation through either infarct, fibrosis, or abnormal nidation. These formations are analogous to the "jet lesions" observed in ventricular septal defects. These lesions are tissue alterations resulting from long exposure to pulsatile blood flow[21] and may have been formed concurrently or subsequently to the aforementioned neovascularization. The result is carved-out areas within the placenta, which appear as sonolucencies, and serve only as blood flow conduits that will bleed extensively at delivery. An ultrasonographic observation of "hypervascularization" was reported by Mendonca[2] in six cases of abnormally adherent placenta. Although their instruments did not have flow monitoring capabilities, we believe the findings are similar to ours.

We conclude that if this pattern of lacunar blood flow is seen, it may predict abnormally adherent placenta (7/8, 87.5% of the lacunar flow group); large blood losses (mean estimated blood loss of 967 ml in a non-lacunar flow group 2814 ml in the lacunar blood flow group); the need for extensive operative therapy (7/8, 87.5% of the lacunar flow group). We believe the following interventions are reasonable in cases with placental and lacunar blood flow patterns: (1) Inform the patient of possible morbidity and blood loss and the possible need for transfusions, operative therapy, or both. (2) Notify the anesthesiologist of the risk of blood loss and other operative interventions. (3) Obtain prior consent for uterine or hypogastric artery ligation or cesarean hysterectomy.

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Transplacental transfer of zidovudine in the near-term pregnant baboon

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Approximately one third of infants born to human immunodeficiency virus type 1 seropositive mothers have evidence of infection or of acquired immunodeficiency syndrome by the age of 18 months. One fifth of infected infants also have died by age 18 months. This prevalence, combined with the demonstration that zidovudine (formerly azidothymidine) can decrease mortality and the frequency of opportunistic infections in patients with acquired immunodeficiency syndrome or acquired immunodeficiency syndrome—related complex, may lead to increasing use of azidothymidine in pregnancy despite a paucity of information regarding its pharmacokinetics. To further investigate the distribution of azidothymidine and its inactive metabolite 5′-glucuronide azidothymidine in the mother, fetus, and amniotic fluid, 12 near-term pregnant baboons were given oral azidothymidine (21 mg/kg/day in four divided doses every 6 hours, equivalent to the usual nonpregnant human dose of 1500 mg/day). Specimens of maternal blood, fetal arterial blood obtained by percutaneous umbilical cord blood sampling, and amniotic fluid were obtained after from one to 17 doses of azidothymidine. Azidothymidine levels were measured by radioimmunoassay with the INCSTAR commercial radioimmunoassay kit and using *Escherichia coli* β-glucuronidase for determination of 5′-glucuronide azidothymidine levels. Paired analyses revealed significant concentration gradients between amniotic fluid, fetal serum, and maternal serum for both azidothymidine ($p < 0.019$) and 5′-glucuronide azidothymidine ($p < 0.002$). The amniotic fluid 5′-glucuronide azidothymidine level increased with increasing doses of azidothymidine despite the fact that the maternal azidothymidine and 5′-glucuronide azidothymidine concentrations were unchanged. This accumulation of amniotic fluid 5′-glucuronide azidothymidine may provide a functional drug reservoir and contribute to the higher fetal concentrations of the medication and its metabolite. Alternatively, the higher fetal levels may represent slower clearance in the fetus than in the mother. Further studies appear warranted with respect to possible adverse fetal effects, especially bone marrow suppression with prolonged and chronic exposure to azidothymidine. (Am J Obstet Gynecol 1990;163:728-32.)

Key words: Azidothymidine, acquired immunodeficiency syndrome, placental transfer

Few disease states have garnered national and international attention and action as quickly as the acquired immunodeficiency syndrome (AIDS). Demand for responsiveness by the scientific and medical community has been intense and action has been prompt. The Food and Drug Administration approved clinical testing of zidovudine (azidothymidine) within 5 days of receipt of its sponsor's application. The review and approval of the zidovudine New Drug Application required only 107 days and clinical studies of only 22 months.[1] Optimism over the demonstration that azidothymidine administration could decrease mortality and the frequency of opportunistic infections in a selected group of subjects with AIDS or AIDS-related complex[2] has resulted in ongoing phase 1 clinical trials of zidovudine in pregnancy. Notwithstanding, published data on azidothymidine in pregnancy, especially in the fetus, are limited to a single study involving one pregnant macaque monkey.[3] In an acute preparation involving intravenous administration of zidovudine (44.1 μg/kg/min) for 3½ hours before cesarean birth, azidothymidine was demonstrated to cross the placenta with a ratio of the steady-state concentration of the drug in fetus/mother of 0.74. To more closely approximate the usual therapy used in actual clinical practice, we administered the drug per os to 12 pregnant baboons, in the third trimester of pregnancy. Because the drug is metabolized in the liver by attachment of glucuronic acid in the 5′ position with subsequent renal excretion of both the free and conjugated drug, the ability of the fetus to metabolize the drug might be impaired by delayed maturation of the glucuronide enzyme system.

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Indeed, in nonpregnant adults with concurrent acetaminophen and azidothymidine treatment, a higher frequency of hematologic complications have been reported and attributed to increased azidothymidine toxicity as a result of competitive inhibition of hepatic metabolism by the glucuronide system.[4] Accordingly, information on the degree to which azidothymidine and its metabolite 5′-glucuronide azidothymidine cross the placenta and the levels achieved in the fetus and the amniotic fluid with prolonged long-term therapy is of great importance in assessment of its toxicity and in evaluation of the relative risk/benefit ratio of treatment during pregnancy.

Material and methods

Twelve near-term pregnant baboons *(Papio cyanocephalus)* with a mean gestational age of 169.6 ± 9.0 days were identified for this study after approval by the Animal Use and Care Committee and Investigational Review Committee of the respective institutions. Each animal was studied only once to reduce the effects of anesthesia on the dam and her fetus. The animals had received from one to 17 doses of azidothymidine when studied (Table I). Oral zidovudine was given to the animals in a dose of 100 mg every 6 hours; the powder was mixed with peanut butter or jelly and ingestion by the animals was observed. The dose was selected to approximate that reported by Fischl et al.[2] of 250 mg every 4 hours for a total daily dose of 1500 mg. If the average weight of a pregnant woman is assumed to be 70 kg, this would be equivalent to 21.4 mg/kg/day. Because of variance in the weight of the animals, the actual mean dose was 22.9 ± 2.3 mg/kg/day of azidothymidine (range, 19.9 to 26.5 mg/kg/day) (Table I).

After initial sedation with ketamine hydrochloride all animals were intubated and a surgical level of anesthesia was maintained with a combination of nitrous oxide and halothane. Maternal stability was ensured by continuous monitoring of heart rate and rhythm and of arterial blood pressure via a radial arterial catheter. Assessment of the fetal heart rate was by ultrasonographic visualization. The maternal abdomen was sterilely prepped and draped; amniocentesis and percutaneous umbilical cord sampling were performed under ultrasonographic guidance as previously reported.[5] In each instance the fetal umbilical artery was sampled; visual identification of the umbilical artery was verified by performing a blood gas analysis on the specimen obtained. A 3 ml aliquot of fetal blood and 10 ml of maternal blood were obtained simultaneously. In each instance the amniotic fluid (7 ml) was obtained before the percutaneous umbilical cord blood sampling to avoid contamination with either maternal or fetal blood.

Both maternal and fetal blood were centrifuged and the serum was separated and labeled. The samples were stored at −70° C pending analysis for azidothymidine and 5′-glucuronide azidothymidine levels. Amniotic fluid was frozen without centrifugation; in each instance the fluid was clear and free of contamination with either blood or meconium.

Table I. Number of doses of oral azidothymidine and weight-adjusted daily dosage

Animal No.	*Doses*	*Weight (kg)*	*Dosage (mg/kg/day)*
1	1	19.6	20.4
2	1	17.9	22.3
3	4	15.1	26.5
4	5	19.4	20.6
5	8	15.9	25.2
6	9	19.4	20.6
7	9	16.5	24.2
8	12	16.9	23.7
9	13	15.9	25.2
10	16	20.1	19.9
11	17	19.3	20.7
12	17	16.0	25.0
		17.67 ± 1.7	22.9 ± 2.3

All assays for azidothymidine were performed by the Wellcome Research Laboratories by radioimmunoassay with the INCSTAR commercial radioimmunoassay kit. Each specimen was analyzed both before and after incubation with *Escherichia coli* β-glucuronidase; the initial value represented the unconjugated azidothymidine level and the value after incubation represented the total (conjugated and unconjugated azidothymidine) level. The 5′-glucuronide azidothymidine concentration was obtained by subtracting the initial azidothymidine concentration from that after incubation with the β-glucuronidase.[6]

Statistical methods. Evaluation of the relative concentrations of azidothymidine in maternal serum, fetal serum, and amniotic fluid were compared with paired analyses. Similar comparisons were also done for 5′-glucuronide azidothymidine concentrations. The effect of increasing number of doses of azidothymidine on azidothymidine and 5′-glucuronide azidothymidine concentrations was studied by linear regression analysis of azidothymidine and 5′-glucuronide azidothymidine levels in maternal serum, fetal serum, and amniotic fluid. An alpha error <0.05 was considered statistically significant and corrections for multiple comparisons were used as indicated.

Results

The mean azidothymidine concentration in maternal serum (58.6 ± 62.5 ng/ml), fetal serum (78.4 ± 79 ng/ml), and amniotic fluid (254.4 ± 107.8 ng/ml) is shown in Fig. 1; the concentration progressively increased from mother to fetus to amniotic fluid. Similar gradients were observed with 5′-glucuronide azido-

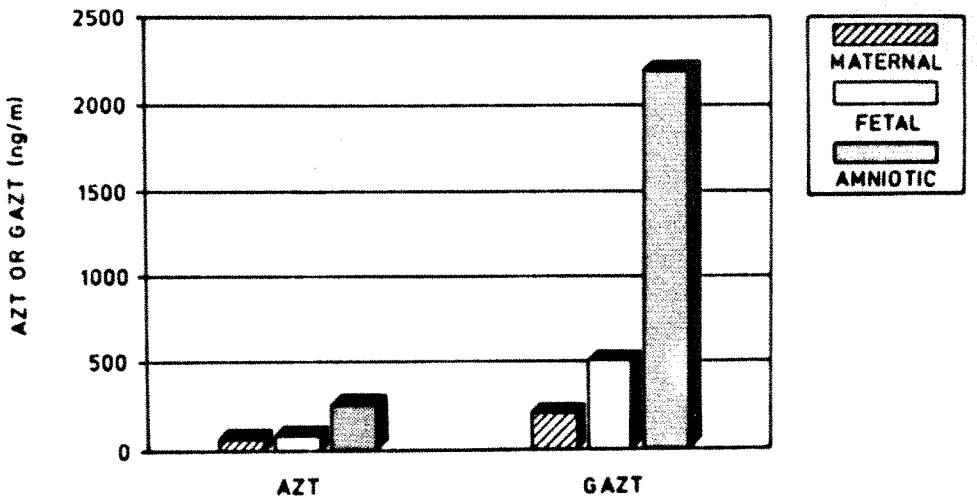


Fig. 1. Azidothymidine and 5′-glucuronide azidothymidine concentrations in maternal serum, fetal serum, and amniotic fluid in near-term pregnant baboons after oral administration of azidothymidine. A clear concentration gradient was present with progressively higher levels being attained in maternal serum, fetal serum, and amniotic fluid ($p < 0.0001$).

thymidine; the maternal serum value was 203.9 ± 189.9 ng/ml, the fetal serum value was 511.8 ± 399.3 ng/ml, and the amniotic fluid value was 2194.1 ± 1208.2 ng/ml. In the evaluation of each individual animal, in only one instance did the maternal azidothymidine level exceed that of the fetus ($p = 0.019$). That particular animal received eight doses of azidothymidine. Amniotic fluid azidothymidine levels exceeded those in maternal serum in all 12 animals ($p < 0.0001$) and exceeded those in the fetus in 11 of 12 animals ($p < 0.0001$). The single exception was an animal that had received only one dose of azidothymidine approximately 3 hours before sampling. In this particular animal the maternal concentration was 144 ng/ml, fetal concentration 163 ng/ml, and maniotic fluid concentration 147 ng/ml. The concentration of azidothymidine in maternal serum, fetal serum, or amniotic fluid showed no apparent relationship to the number of doses received (p = NS), especially within the range of four to 17 doses (Fig. 2).

Similar to the findings with azidothymidine, 5′-glucuronide azidothymidine levels in the fetus exceeded those in the mother in 11 of 12 animals ($p = 0.002$), and amniotic fluid concentrations greatly exceeded those in the maternal serum in all cases ($p < 0.0001$). Amniotic fluid 5′-glucuronide azidothymidine levels exceeded those of the fetus in 11 of 12 animals ($p = 0.0004$); the one exception was the animal that had received only one dose of azidothymidine approximately 3 hours before sampling. In this animal the maternal 5′-glucuronide azidothymidine level was 410 ng/ml, the fetal level was 852 ng/ml, and the amniotic fluid level was 651 ng/ml. There was no detectable change in maternal or fetal circulating concentrations with increasing numbers of doses (p = NS). Significantly, the concentration of 5′-glucuronide azidothymidine in amniotic fluid did show a positive correlation with the number of doses of medication the animals had received before sampling ($p < 0.01$) (Fig. 3).

Comment

The full impact of AIDS on women and children in the United States remains a future, but certain, event. Currently the reported cases of AIDS in children in the United States are <2% of the number in adults,[7] and serologic prevalence of human immunodeficiency virus among childbearing women remains low (2.1/1000).[8] However, this is not universally the case; Ryder et al.[9] reported that 5.8% of pregnant women screened in Zaire were seropositive for human immunodeficiency virus type 1. By 1 year after delivery 21% of infants of seropositive women were dead compared with 3.8% of control infants whose mothers tested negative. Furthermore, 7.9% of the surviving infants had AIDS by the age of 1 year. Similar results have been reported by the French Collaborative Study Group[10] who found that approximately one third of the infants born to seropositive women had evidence of human immunodeficiency virus type 1 infection or of AIDS by age 18 months and that 20% of this group had died.

Treatment of pregnant women with medications potentially toxic to both the woman and her fetus raises several questions: Who is being treated and what are the indications for treatment? Does the fetus possess certain characteristics that may either augment or protect it from drug toxicity? To what extent does the drug

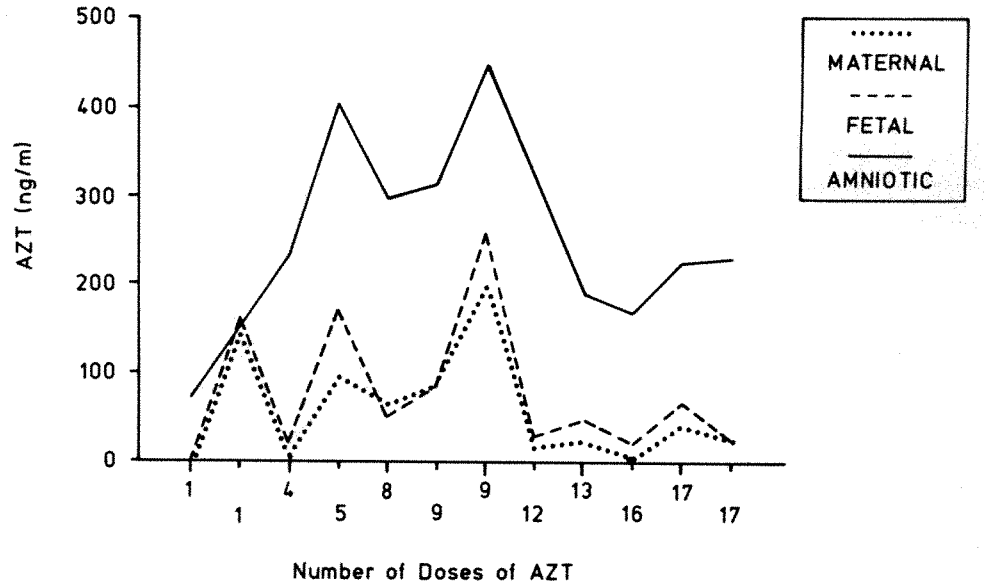


Fig. 2. Azidothymidine concentrations in maternal serum, fetal serum, and amniotic fluid versus the number of doses of azidothymidine. The concentration of azidothymidine was not altered significantly in any of the three compartments with increasing numbers of doses of azidothymidine.



Fig. 3. 5′-Glucuronide azidothymidine concentrations in maternal serum, fetal serum, and amniotic fluid versus the number of doses of azidothymidine. 5′-Glucuronide azidothymidine amniotic fluid concentrations rose with increasing dosages of azidothymidine ($p < 0.01$), whereas maternal and fetal serum levels remained unchanged.

cross the placenta and can maternal drug levels be used to extrapolate to fetal drug levels? In the case of azidothymidine many, if not all, of these questions remain unanswered. Indeed, to date it has not been established whether fetal infection occurs principally in utero by transplacental routes, as occurs with intrauterine rubella, or intrapartum as with the hepatitis B virus.[7]

By use of an animal model with placentation similar to that of humans, we found that the serum concentrations of both azidothymidine and 5′-glucuronide azidothymidine were higher in the fetus than in the mother, irrespective of the number of doses of oral medication the mothers had ingested. After intravenous dosing with azidothymidine in nonpregnant adults, the compound has glucuronic acid attached in the 5′ position in the liver, thereby inactivating a large

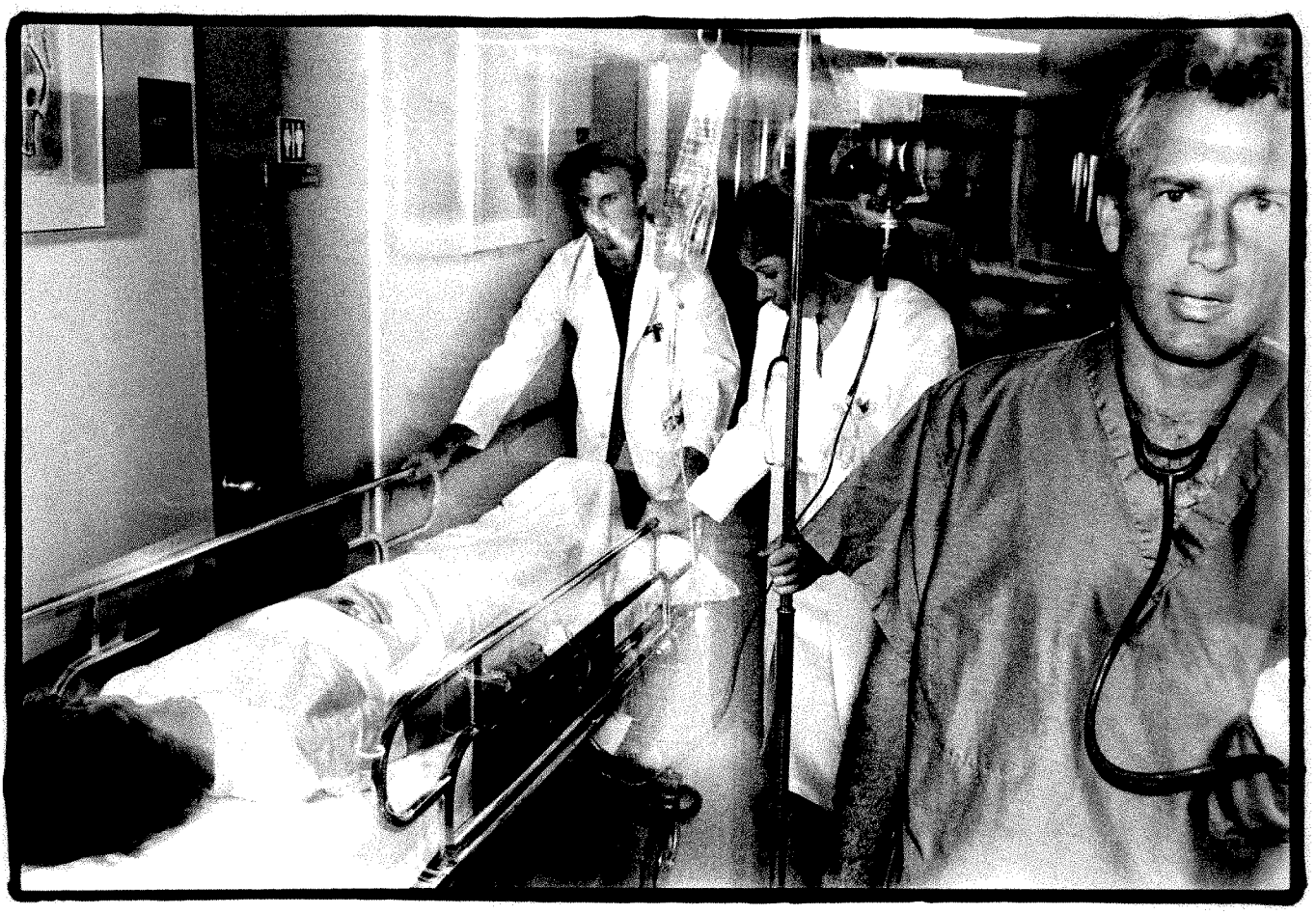
percentage of the drug. Further metabolism involves renal clearance; 60% of the drug is excreted in the urine as 5′-glucuronide azidothymidine and 25% as azidothymidine.[11] The increased fetal/maternal ratio of the drug may result from an impaired ability to conjugate the drug by the fetal liver because it is well established that this particular enzyme system does not mature until well after birth. In addition, renal clearance of azidothymidine in the newborn, and by extrapolation of the fetus still in utero, is markedly depressed in relation to that of adults and does not approach the same rate until several days of life.[3] Alternatively, and perhaps synergistically, the high concentrations of both azidothymidine and its metabolite in the amniotic fluid may serve as a source of oral therapy for the fetus via in utero swallowing and absorption. A role for fetal swallowing in the further metabolism of amniotic fluid azidothymidine is supported by the fact that the amniotic fluid azidothymidine concentration did not increase in proportion to the number of doses, whereas concentration of its metabolite 5′-glucuronide azidothymidine did increase (Fig. 3).

With prolonged courses of azidothymidine treatment Richman et al.[4] observed that in 24% of patients anemia developed, defined as a hemoglobin level <7.5 gm/dl, compared with only 4% of patients treated with placebo. Twenty-one percent of azidothymidine recipients and 4% of placebo recipients required multiple red cell transfusions with hematologic toxicity apparently augmented by concurrent use of acetaminophen. Such toxicities may be even more common and severe in the setting of very active bone marrow, such as characterized by both the pregnant woman and her fetus. A parallel between the effects of acetaminophen in the adult and the immature liver of the fetus should be anticipated with respect to more intense hematologic toxicity. Continued usage of these drugs in pregnancy before further detailed animal studies would seem at a minimum to merit intense ultrasonographic surveillance for the potential development of severe fetal anemia and hydrops.

In conclusion, on the basis of data obtained from the pregnant baboon, the fetal levels of azidothymidine will equal or exceed those in the mother. It is anticipated that azidothymidine toxicity in pregnancy, for both mother and fetus, will equal (or exceed) that of nonpregnant patients. We concur that "the priority given studies of possible intrauterine, or neonatal interventions, whether pharmacologic or immunologic, to combat human immunodeficiency virus infection should remain exceedingly high."[7]

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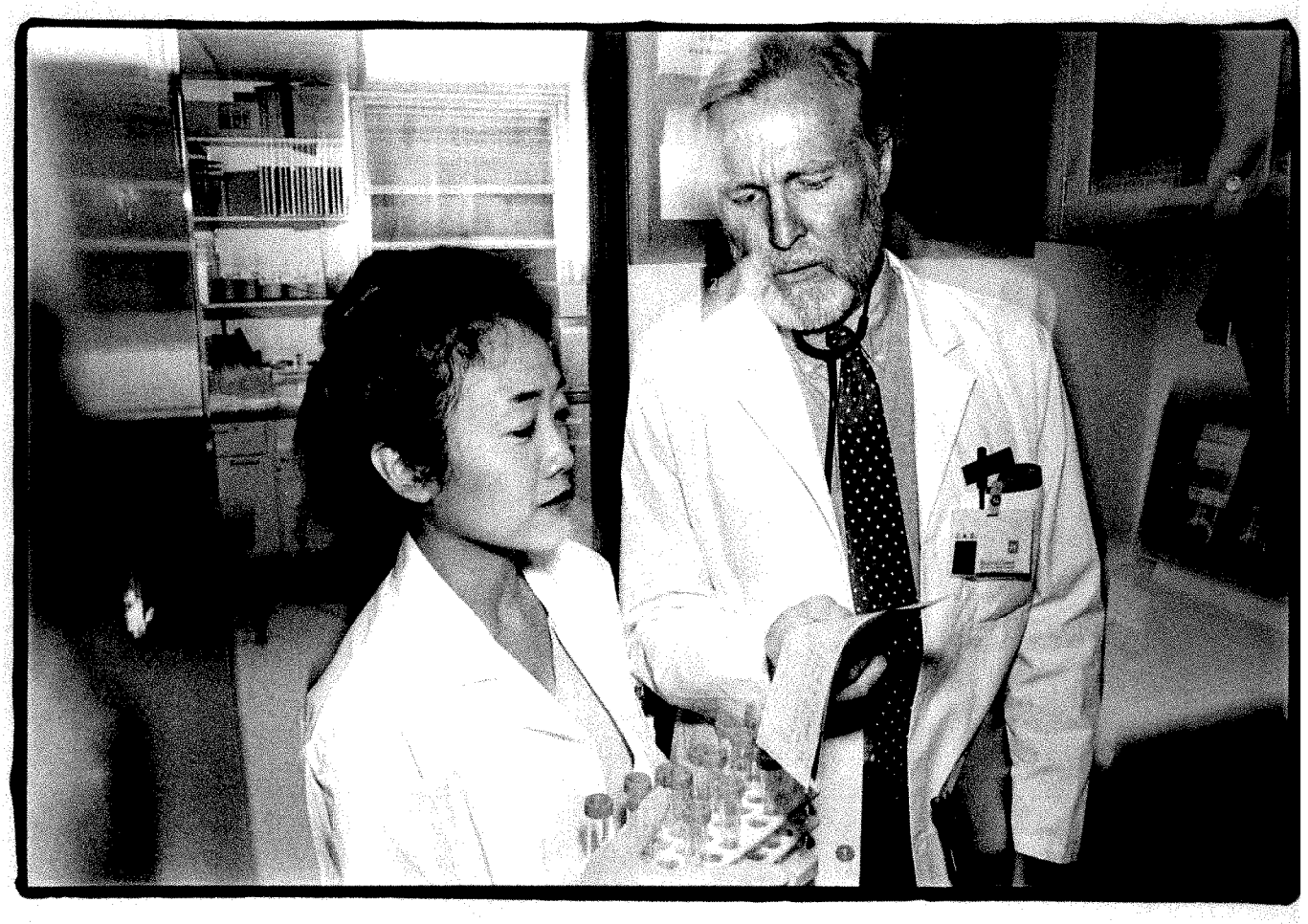
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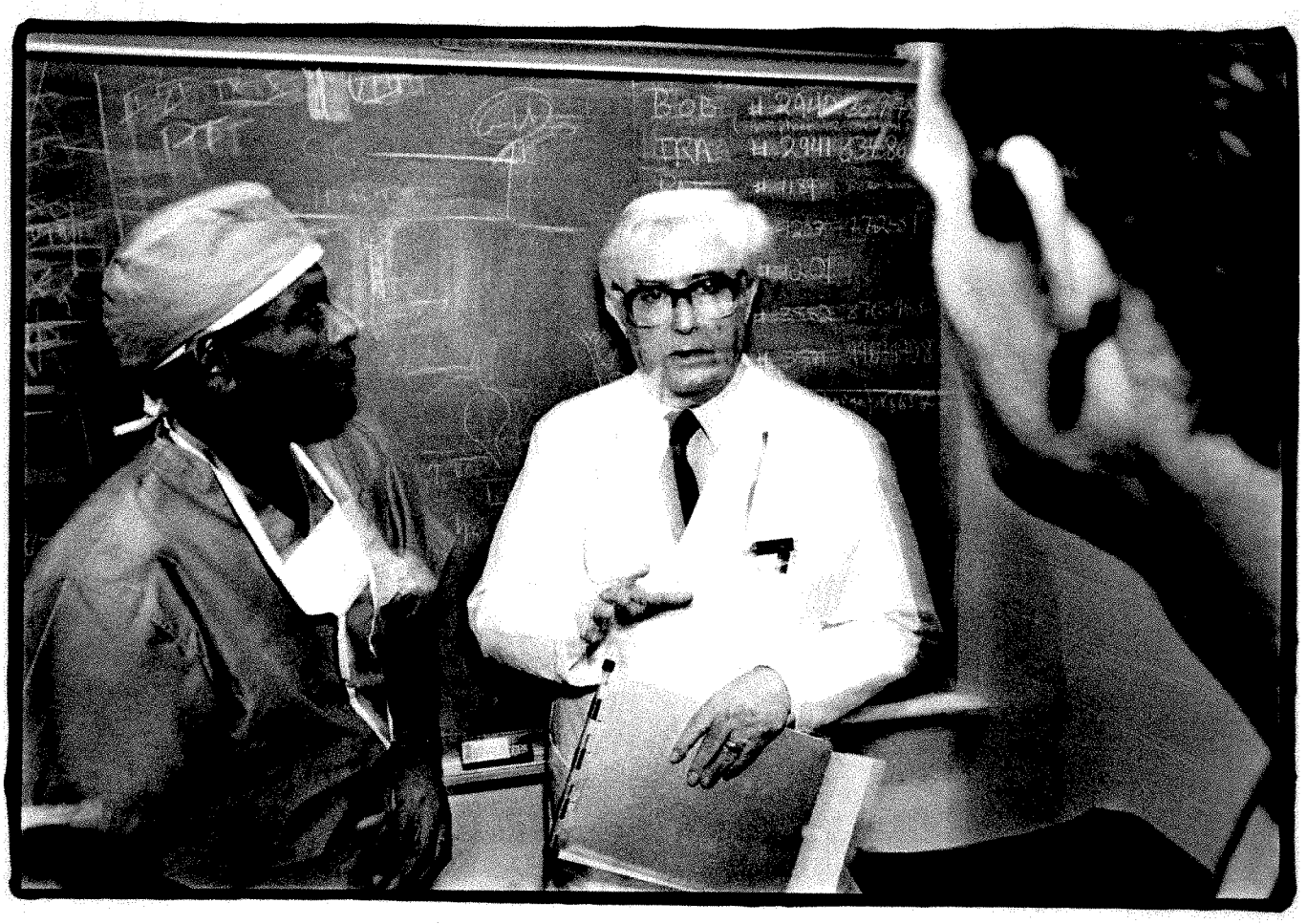
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"We need gold-standard results that don't cost a fortune."

Lower antibiotic costs without lowering your standards. UNASYN costs at least 40% less per day than clindamycin/gentamicin or cefoxitin.[11] Yet UNASYN is at least as effective in a variety of mixed infections.*[3,12-19]

And in some studies versus combination therapy, patients treated with UNASYN spent fewer days in the hospital.[3,16,17]

So, look to UNASYN for highly effective, highly affordable therapy in mixed infections* every day.

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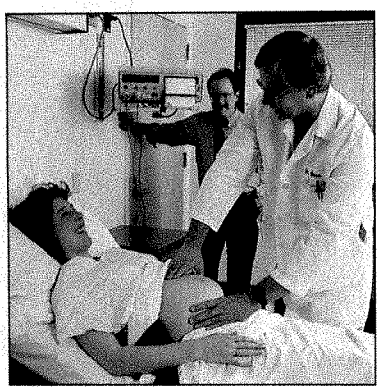
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Walnut Creek — Department of 15 physicians, a perinatologist and seven nurse practitioners. Two physicians on call daily. Teaching responsibilities for third year residents affiliated with the University of California at San Francisco. Clinical appointments at UCSF also available. Expansion plans include a large ICN, and within five years, a completely new hospital.

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Vallejo/Fairfield/Napa — Seventeen physicians and four nurse practitioners at these facilities. Approximately 2,900 deliveries performed each year at the Vallejo medical center. Usual call is every eighth night. Affiliated with David Grant Medical Center residency program at Travis Air Force Base. Our area offers diverse lifestyle options, with both recreational and cultural attractions nearby.

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A protocol for managing severe preeclampsia in the second trimester

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One hundred nine patients with severe preeclampsia in the second trimester were studied. Pregnancy termination was recommended for those with gestational age ≤24 weeks (n = 25), whereas expectant management with aggressive maternal and fetal monitoring was recommended for those with gestational age >24 but ≤27 weeks (n = 84). Ten of the 25 women in the early pregnancy group accepted termination and 15 elected to continue the pregnancy. The overall perinatal survival in the latter 15 patients was 6.7%, and maternal complications developed in six patients. Thirty of the 84 patients in the late second-trimester group had immediate delivery, and 54 had expectant management. The average length of pregnancy prolongation in the expectant group was 13.2 days (range, 4 to 28 days). Compared with the immediate delivery group, the expectant management group had significantly higher perinatal survival (76.4% versus 35.%), significantly higher birth weights (880 versus 709 gm), and a lower incidence of neonatal complications. There were no differences between the two groups with regard to maternal complications. Expectant management with aggressive monitoring of maternal and fetal status at a perinatal center improves perinatal outcome in patients with severe preeclampsia with gestational age >24 but ≤27 weeks. (Am J Obstet Gynecol 1990;163:733-8.)

Key words: Preeclampsia, second trimester, expectant management

Severe preeclampsia that develops in the second trimester is associated with high perinatal mortality and morbidity.[1-3] Aggressive management with immediate delivery results in high neonatal mortality. In addition, significant neonatal complications develop in all surviving newborn infants and prolonged hospitalization in neonatal intensive care units is necessary. Moreover, a significant proportion of surviving infants have long-term disability.[1,4] Conversely, attempts to prolong pregnancy may result in fetal death or asphyxial damage in utero.[1,3]

We previously reported on 60 such pregnancies that had conservative management in an attempt to prolong pregnancy. The overall perinatal survival was only 13%. However, for patients who had the disease before 25 weeks' gestation, the survival rate was 3.2% (1/31), whereas it was 27.6% (9/29) for patients in whom the disease developed at or beyond 25 weeks' gestation. In addition, maternal morbidity was significant with the majority of complications in patients in whom the disease developed early in the second trimester and in patients who had conservative management at local hospitals before referral to the perinatal center. As a result, a new protocol for management of these patients was initiated in 1985. The purpose of this article is to report pregnancy outcome in 109 such patients since the institution of this new protocol at this center.

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6/6/22348

Material and methods

The study included 109 patients with severe preeclampsia developing at or before 27 weeks' gestation who were managed at the E. H. Crump Women's Hospital and Perinatal Center between January 1985 and June 1989. Severe preeclampsia was defined as reported previously from this center.[2] All patients had a live fetus at the time of inclusion, and all had documented evidence of the disease for less than 48 hours before this management. Patients with maternal or fetal indications necessitating immediate delivery on admission were not included. For example, patients with thrombocytopenia (platelet count $<10 \times 10^3/mm^3$, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, pulmonary edema, evidence of fetal distress, oligohydramnios) were excluded. In addition, patients who were managed conservatively at a local hospital before transfer to the center were also excluded. Most patients in this group required immediate delivery for maternal or fetal indication as stated above.

All patients were first admitted to the labor and delivery area and carefully evaluated. They were then counseled regarding maternal and perinatal risks and benefits from expectant management. Pregnancy ter-

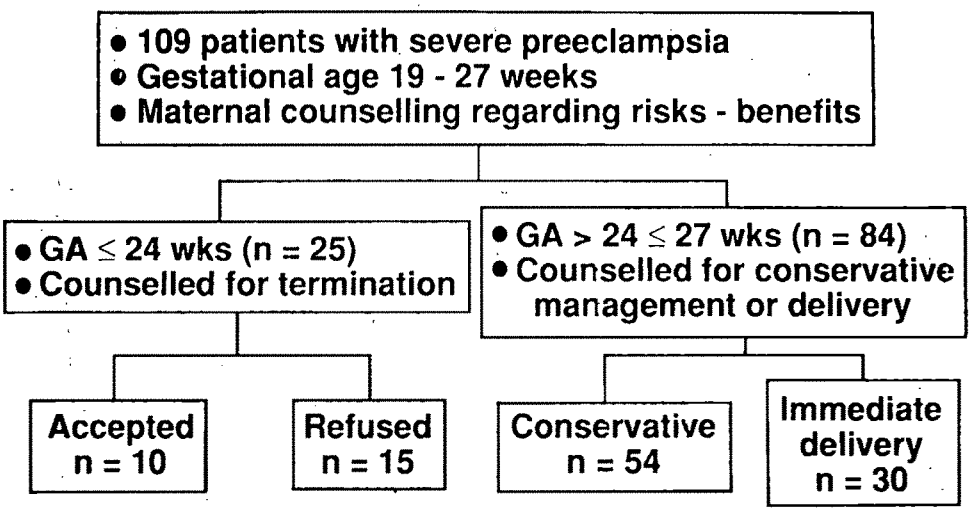


Fig. 1. Summary of 109 patients with severe preeclampsia. Patients were counseled with regard to termination or expectant management on basis of gestational age at time of admission.

mination was recommended for patients with gestational ages ≤24 weeks; aggressive expectant management monitoring was recommended if the gestational age was >24 but ≤27 weeks. The study patients were then subdivided into four groups (Fig. 1). One group (n = 10) with gestational age ≤24 weeks accepted immediate termination of pregnancy. These patients received intravenous magnesium sulfate to prevent convulsions, intravenous hydralazine to control severe hypertension, and prostaglandin E vaginal suppositories to terminate pregnancy. A second group (n = 15) with similar gestational age elected to continue with expectant management.

A third group (n = 30) with gestational age >24 weeks had immediate delivery either because of patient's desire (n = 21) or because of attending staff desire (n = 9). These patients had stabilization of maternal condition, continuous monitoring in labor and delivery, and received corticosteroids to accelerate fetal lung maturity. They were then delivered 24 hours after the last dose of steroids if possible. The remaining patients (n = 54) with gestational age >24 weeks elected expectant management.

Patients who chose conservative management were monitored in the labor and delivery area for a minimum of 24 hours. Initial drug therapy consisted primarily of intravenous magnesium sulfate to prevent convulsions and bolus injections of hydralazine or labetalol to maintain diastolic blood pressure below 100 mm Hg. Intravenous fluids and urinary output were carefully monitored during the observation period. After this observation period patients were then transferred to the high-risk antepartum floor. Oral antihypertensive medications were then used to maintain the diastolic pressure between 90 and 100 mm Hg. The antihypertensive drugs used were methyldopa, hydralazine, and labetalol initially; nifedipine was used during the last 2 years of the study.

Fetal viability was confirmed on admission in all cases. Gestational age was determined by the combined use of last menstrual period and early ultrasonographic measurements. Fetal growth was measured ultrasonographically every 10 to 14 days when appropriate (in patients continuing their pregnancies beyond this point). The presence of severe fetal growth retardation (estimated fetal weight <5th percentile for our population) was considered a fetal indication for delivery. Fetal well-being was assessed by daily biophysical profile and nonstress testing. The biophysical profile was evaluated according to the criteria of Manning et al.[5] The biophysical profile was considered abnormal if the score was ≤4/8 on two occasions 6 hours apart. Because the nonstress test is nonreactive in the majority of fetuses with these gestational age, the reactivity of the nonstress test was not considered in the biophysical profile. Thus the total score used was 8. The nonstress test was considered abnormal if the test was nonreactive in association with persistent spontaneous decelerations. The presence of either an abnormal nonstress test result or an abnormal biophysical profile score was considered a fetal indication for delivery. Corticosteroids were used routinely to accelerate fetal lung maturity in all cases when the gestational age was >25 weeks.

Maternal evaluation included frequent blood pressure measurements and daily weight. All patients were instructed to report the presence of persistent headaches, visual disturbances, or epigastric pain. In addition, they were instructed to report the presence of uterine contractions, abdominal pain, vaginal bleeding, or significant changes in fetal movements (absent fetal

Table I. Group with gestational age ≤ 24 weeks who refused termination (n = 15)

	Mean ± SD	*Range*
Gestational age at onset (wk)	22.1 ± 1.3	19-23.5
Gestational age at delivery (wk)	24.8 ± 1.8	22.3-27
Pregnancy prolongation (days)	19.4 ± 11.6	5-42
Birth weight (gm)	437 ± 164	80-740

Table II. Pregnancy outcome in women who refused termination

	No.	*%*
Stillbirths	11	73.3
Neonatal deaths	3/4	75
Perinatal survival	1	6.7
HELLP syndrome	3	20
Abruptio placentae	2	13.3
Eclampsia	1	6.7

movements for 4 hours during the day). The presence of absent fetal movement was evaluated by the nonstress test and biophysical profile and was then managed according to the findings of these tests. Laboratory evaluation included serial measurements of creatinine clearance and 24-hour excretion of protein. All patients also had daily measurements of hematocrit, platelet count, coagulation profile, and liver enzymes levels. Thrombocytopenia was defined as a platelet count of $<100 \times 10^3/mm^3$. The combination of hemolysis, elevated liver enzymes, and low platelet count was defined as the HELLP syndrome as described previously from this center.[6] Maternal indications for delivery included the development of convulsions, thrombocytopenia only, HELLP syndrome, pulmonary edema, vaginal bleeding (in absence of placenta previa), and persistent epigastric pain.

Clinical data on the infants included gestational age, birth weights, Apgar scores, cord blood gases, and neonatal complications. An infant was considered to be small for gestational age if the birth weight was below the 10th percentile according to the criteria of Brenner et al.[7] All newborn infants were followed up until discharge from the intensive care nursery. Surviving infants were subsequenty seen at our follow-up clinic and interval history and physical examination was available at each visit. Children with diagnosed cerebral palsy or hydrocephalus were considered neurologically abnormal; all others were considered to have normal development.[4]

For comparative purposes pregnancy in patients with gestational age >24 weeks was compared with the respective outcome in the patients with similar gestational age who had immediate delivery. Results were analyzed by Student's t test to compare means of normally distributed data, χ^2 test to compare frequencies, and Fisher's exact test when appropriate. Differences were considered to be significant for values of $p < 0.05$.

Results

During the period of this study 121 patients with severe preeclampsia that developed in the second trimester were delivered at this center. Twelve patients required immediate delivery on admission for either maternal or fetal reasons. Three patients presented with eclampsia, three had HELLP syndrome, one had pulmonary edema, one had severe thrombocytopenia, three had abruptio placentae, two had fetal death on admission, and four had evidence of fetal distress (some patients had more than one complication). The average gestational age at time of delivery in these patients was 25.2 weeks (range, 20 to 27 weeks). These pregnancies resulted in 5 stillbirths and six neonatal deaths (overall perinatal survival of 8.3%).

Ten patients with gestational age ≤24 weeks accepted termination of pregnancy and thus received prostaglandin E_2 vaginal suppositories. All pregnancies resulted in stillbirths and there were no maternal complications in this group. The mean gestational age in these 10 patients was 21.8 weeks (range, 18 to 23.5 weeks), and the mean birth weight was 422 gm (range, 210 to 580 gm). There was no evidence of hydropic degeneration of the placenta in any of these pregnancies.

Fifteen patients with gestational age ≤24 weeks chose expectant management. Tables I and II summarize the gestational age at time of onset of the disease, gestational age at time of delivery, and the overall maternal and perinatal outcome in these patients. There were 11 stillbirths and three neonatal deaths (overall perinatal survival of 6.7%) in these patients. The three neonatal deaths occurred in infants with birth weights of 440, 470, and 650 gm. The surviving infant had a birth weight of 740 gm and stayed in the neonatal intensive care unit for 95 days. This infant had normal findings on follow-up at 4 years. In addition, four patients (27%) had one or more of the maternal complications listed in Table II.

Of the 84 patients with severe preeclampsia at >24 weeks' gestation 54 had conservative management and 30 had immediate delivery (Fig. 1). The groups were similar with regard to maternal age (23.8 ± 6.3 vs 23.0 ± 6.0 years), percent nulliparous (63% vs 59%), and frequency of chronic hypertension (33% vs 30%).

Table III compares the pregnancy outcome in these patients. Except for the one patient with fetal death, all pregnancies were delivered by cesarean section. The conservative management group had significantly

Table III. Pregnancy outcome

Variable	*Conservative group (n = 54)*	*Immediate group* (n = 30)*	*p Value*
Admission GA (wk)	26.1 ± 0.9	26.0 ± 0.9	
Delivery GA (wk)	28.0 ± 1.2	26.3 ± 0.8	<0.0001
Prolongation (days)	13.2 ± 8.1	2.0 ± 0.2	<0.0001
Birth weight (gm)	880 ± 212	709 ± 159	<0.0001
Placental weight (gm)	289 ± 78	255 ± 74	NS
Perinatal death (no., %)	13 (23.6)	20 (64.5)	<0.0005
Apgar score			
1 min	4.1 ± 2.5	2.9 ± 2.1	<0.03
5 min	6.6 ± 1.9	5.4 ± 2.3	<0.01
Cord pH	7.26 ± 0.07	7.20 ± 0.11	<0.01
Days in NICU†	70 ± 32	115 ± 94	<0.02

GA, Gestational age; *NICU*, neonatal intensive care unit.
*31 infants (one twin gestastion).
†For neonatal survivals only.

Table IV. Neonatal complications

Complication	*Conservative group (n = 54)*		*Immediate group (n = 31)*	
	No.	*%*	*No.*	*%*
Small for gestational age	26	48	10	32
Respiratory distress syndrome	32	60	26	84
Intraventricular hemorrhage	22	41*	22	71*
Bronchopulmonary dysplasia	18	33	6	19
Necrotizing enterocolitis	5	9	5	16
Seizures	3	5	5	16

*$p < 0.007$, odds ratio 3.6 : 1.

higher mean gestational age and birthweight at time of delivery. The 54 pregnancies in the conservative group resulted in 55 births (one set of twins). There was one stillbirth and 12 neonatal deaths (overall perinatal loss of 23.6%) in this group. The 30 pregnancies in the immediate delivery group resulted in 31 births (one set of twins). There were no stillbirths in this group, and the overall neonatal loss was 64.5%. Thus the conservative treatment group had a significantly higher perinatal survival than the immediate delivery group (76.4% vs 35.5%, $p < 0.0005$). In addition, the conservative group had a significantly higher Apgar score and pH, and a significantly lower number of days in the newborn center than the immediate delivery group.

Table IV compares the neonatal complications between the two groups. The conservative group had a significantly lower incidence of neonatal intraventricular hemorrhage than the other group (41% vs 71%, $p < 0.007$). The conservative group also had a lower incidence of neonatal seizures (5% vs 16%); however, this difference was not significant.

There were 42 surviving infants in the conservative treatment group with a mean (±SD) follow-up of 21.8 ± 15 months (range, 3 to 48 months). Five infants (11.9%) had significant neurologic deficits. Eleven surviving infants in the immediate group had follow-up of 18.3 ± 16.1 months (range, 3 to 48 months). Three (27.3%) had significant neurologic deficits. The difference between the two groups was not significant because of the small number of infants in each group.

Maternal outcome. Maternal complications were the indication for delivery in 12 women (22.2%) in the conservative management group. The remaining patients were delivered for fetal indications. These 12 patients had a total of 17 complications (HELLP syndrome, eclampsia, abruptio placentae, or thrombocytopenia). Conversely, six patients (20%) in the immediate delivery group had a total of eight similar maternal complications. Table V compares the maternal complications between the two groups. There were no differences regarding any of the categories studied.

Comment

Severe preeclampsia in the second trimester is an infrequent complication of pregnancy. Most practicing obstetricians have limited experience in managing such patients. Pregnancy outcome in these patients depends on gestational age at time of onset of the disease, as well as maternal and fetal status at time of presentation to a perinatal center.[1, 4, 8] Optimum management

usually depends on balancing the risks to the mother and fetus from expectant management against the risks of extreme prematurity from immediately delivery.

This study was designed to evaluate a new protocol for management of such patients that depended on the gestational age at time of onset of severe preeclampsia. Pregnancy termination was recommended for the 25 patients who had the disease at ≤24 weeks' gestation; however, 15 (60%) refused such recommendation. As a result these patients require aggressive monitoring of maternal and fetal status and thus should be referred to a perinatal center with adequate maternal and neonatal intensive care facilities. The overall perinatal survival rate in these patients was only 6.7% (1/15), and maternal morbidity was significant (27%). These findings argue against any potential benefit from conservative management in these patients. The findings are in agreement with our prevoiusly reported experience.[1] In addition. Odendaal et al.[3] reported a zero perinatal survival rate after conservative management in 11 such patients.

Conservative management was recommended for the 84 patients who had the disease at >24 but ≤27 weeks' gestation; however, 30 (36%) had immediate delivery because of refusal of conservative management either by the patient or by the attending physician. This study demonstrated that it was possible to prolong pregnancy by an average of 2 weeks (range, 4 to 38 days) in the group who had conservative management. This prolongation in pregnancy was associated with significant improvement in both perinatal mortality and morbidity without a significant increase in maternal morbidity when compared with the group who had immediate delivery. The perinatal survival rate in the expectant group was 76.4% compared with 35.5% in the group that had immediate delivery. In addition, the infants in the conservative management group had a lower incidence of intraventricular hemorrhage (41% vs 71%) and a lower number of days in neonatal intensive care unit (70 vs 115 days). In this study a small number of infants in both groups had a follow-up period beyond 2 years of age. As a result we restricted our comparisons to the presence of significant neurologic deficit. Thus our data cannot be used to draw any conclusions with regard to any differences between the two groups as it relates to the presence of subtle or minimal neurologic abnormalities. It is interesting to note that the conservative group had a higher incidence of bronchopulmonary dysplasia (33%) than the immediate group (19%). This difference may be a result of the fact that 11 infants in the immediate group died within 1 week of delivery (before the onset of bronchopulmonary dysplasia). Conversely, only three infants in the conservative treatment group died within 1 week of delivery.

Table V. Maternal complications

Variable	*Conservative group (n = 54)*		*Immediate group (n = 30)*	
	No.	*%*	*No.*	*%*
HELLP syndrome	7	13.0	4	13.3
Eclampsia	3	5.6	1	3.3
Abruptio placentae	3	5.6	2	6.7
Thrombocytopenia only	4	7.4	1	3.3

It is important to note that delivery was delayed >1 week in 39 patients and >2 weeks in 18 patients in the conservative management group. A gain of 1 to 2 weeks before delivery could have been of great benefit for fetuses with gestational ages between 24 and 25 weeks. In these pregnancies a gain of 2 weeks could have been the difference between a live infant with intact survival or an imminent neonatal death. These data should be useful in counseling such patients.

Our findings indicate that the nonstress test and the biophysical profile are reliable in assessing the fetal condition during conservative management in the group with gestational age >24 weeks. In this study monitoring was started as soon as the patient was admitted and performed daily regardless of gestational age. Among the 54 pregnancies that had this intensive monitoring, there was only one fetal death from abruptio placentae. Conversely, the diagnosis of abruptio placentae was suspected and later confirmed in two other patients who demonstrated repeat decelerations during the nonstress test. It is important to note that 42 (78%) of the pregnancies in this group were delivered for fetal indications as determined by the biophysical profile or the nonstress test. In addition, it is important to note that the institution of early and intensive fetal monitoring in this study is responsible for the improved perinatal outcome compared with the results reported from this center in an earlier study.[1] An important difference between the two studies is the onset and frequency of fetal monitoring. In the earlier report monitoring was not commenced until 27 weeks' gestation and most perinatal deaths occurred before that time.

In an earlier report[1] we described a high incidence of maternal complications among 60 patients with severe preeclampsia who had conservative management. Significant maternal complications included abruptio placentae (27.7%), eclampsia (16.7%), the HELLP syndrome (16.7%), and acute renal failure (5%). The incidence of abruptio placentae for patients with conservative management in this study was 5.6%, and the incidence of eclampsia was 5.6%. None of the patients had acute renal failure. It is important to emphasize that the institution of early and intensive maternal mon-

itoring in this study is responsible for the improved maternal outcome compared with the results reported in the early study and the results obtained in the 12 patients who required immediate delivery on admission (excluded patients). In the earlier report most patients had conservative management at local hospitals, and patients were not referred until onset of maternal complications. These findings underscore the importance of referring such patients to tertiary care centers with appropriate intensive care facilities once the diagnosis is made.

In summary, the development of severe preeclampsia in the second trimester is associated with high perinatal mortality and morbidity and significant maternal morbidity. Patients should be referred to a tertiary care center once the diagnosis is established. Conservative management with aggressive monitoring of maternal and fetal status is possible in a *select* group of these patients, primarily those with gestational age beyond 24 weeks. This management should be practiced *only* in a tertiary care center with adequate intensive care facilities.

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Catastrophic complications of previous cesarean section

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Of 711 patients who were delivered after one or more previous cesarean sections, 17 (2.4%) had an extremely serious complication. Uterine rupture and placenta previa or placenta accreta with accompanying hemorrhage were the major contributors to mortality and major morbidity. Nine uterine ruptures occurred, including five associated with labor with a low transverse uterine scar and one with an unknown scar (1.4% of trials of labor). There were two cases of placenta previa and five with varying degrees of placenta accreta. The nature and frequency of the observed complications emphasize the potentially serious remote consequences of cesarean section. (Am J Obstet Gynecol 1990;163:738-42.)

Key words: Previous cesarean, uterine rupture, placenta accreta, cesarean complications

Many women with a uterine scar from previous cesarean section become pregnant and are thereby exposed to certain risks. Although there is general agreement that pregnancy and labor after cesarean delivery are reasonable and safe,[1] precise quantification of the risk attributable to a prior cesarean section is difficult. Most studies suggest that uterine rupture or placenta accreta with potentially serious consequences for the mother or fetus occur infrequently.[2-8] As experience with patients with prior cesarean sections has grown, the ability to assess the likelihood of a serious complication in a subsequent pregnancy has been refined. We performed a retrospective analysis to quantify the risk of catastrophic complications in a pregnancy after previous cesarean delivery.

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6/6/22317

Methods

From January 1986 to June 1989 there were 10,835 deliveries at the Bronx Municipal Hospital Center, of which 711 (6.6%) involved patients with a prior cesarean section. Vaginal birth after cesarean section was attempted by 424 women and was successful in 312 (73.6%). We defined a catastrophic complication related to a prior cesarean section as one that resulted in maternal or fetal death; hemorrhage necessitating transfusion of ≥5 units of red blood cells, hysterectomy, or major artery ligation; or uterine rupture necessitating emergency surgery or associated with an extruded fetus or neonatal depression (Apgar score <6 at 5 minutes). The diagnosis of placenta accreta was accepted only if confirmed histologically in an extirpated uterus.

Seventeen (2.4%) women with a previous cesarean section who had one or more catastrophic complications during a subsequent pregnancy were identified from the hospital's computerized discharge data system and the chronologic birth record. The medical records from these 17 cases were reviewed. In addition, one or both authors was involved in the management of most of the complications and was thus familiar with the clinical details.

Results

Among the 17 identified cases with serious complications (Table I), 10 (59%) had a previous low transverse uterine incision. Eight patients (47%) had more than one prior cesarean delivery. Twelve (71%) infants were delivered preterm, and eight required admission to the neonatal intensive care unit.

There were two maternal and three fetal deaths among the study patients (Table II). One mother died from uncontrollable intraoperative hemorrhage during repeat cesarean section. She had an extensive placenta previa and percreta after two prior uncomplicated low-segment cesarean sections. The other maternal death was from a massive pulmonary embolus 4 weeks after cesarean hysterectomy for rupture of a previous vertical uterine scar identified at elective repeat cesarean. Two of the fetal deaths followed uterine rupture with complete extrusion of the fetus into the peritoneal cavity. The third fetal death involved spontaneous exsanguinating maternal hemorrhage at 22 weeks' gestation. This required cervical dilatation and fetal evacuation followed by internal iliac artery ligation and hysterectomy for control. Thirteen units of blood were transfused. The placenta was implanted as a central previa.

Serious hemorrhage occurred in 11 women and necessitated hysterectomy in eight. In three patients the hemorrhage was caused by uterine rupture and in the others by placenta previa, often in association with some degree of placenta accreta. Only two of the hemorrhages occurred during a planned trial of labor. In four of the patients with hemorrhage, all of whom had placenta previa or accreta, bilateral uterine or internal iliac artery ligation was performed; hysterectomy was thus avoided in one case.

Nine of the 17 women with serious complications had uterine rupture; these constituted 1.3% of all patients delivered after one or more previous cesarean sections. Six ruptures were associated with trial of labor (1.4% of all patients who were allowed a trial of labor). Among these six ruptures, five were likely to have occurred during labor. One case was undoubtedly present before induction of labor at 33 weeks for presumed intrauterine fetal death and suspected abruptio placentae. Recognition of the misdiagnosis in this case led to exploratory laparotomy and identification of the rupture and extruded fetus. Three of the five patients whose ruptures probably occurred during a trial of labor had received oxytocin.

In four of the cases of uterine rupture the umbilical cord or entire products of conception were extruded from the uterine cavity; of these cases, two fetuses were stillborn and two had Apgar scores <6 at 5 minutes. In the five cases of rupture in which extrusion did not occur, only one infant had neonatal depression. In six of the nine women with uterine rupture it was deemed appropriate to repair the uterus rather than to perform hysterectomy.

Four of the six ruptures in uteri with prior low transverse incisions appeared to occur along the old scar and extended laterally into the vascular tissue of the broad ligament. One extended vertically from the lateral corner of the old scar cephalad into the fundus and caudad to the cervix. Another extended vertically in the midline. We were unable to determine in this patient whether during the previous surgery the transverse hysterotomy had been extended vertically. The prior incision known to have been vertical ruptured along the scar, and of the two cases in which the prior incision type was unknown, one ruptured vertically and the other both vertically and laterally into the broad ligament.

Comment

We reviewed the incidence and nature of extremely serious complications of pregnancy after cesarean section. Overall, one patient in 42 with one or more prior cesarean deliveries had such a complication. The risk of maternal or fetal death in our series was approximately one in 143 pregnancies with a history of previous cesarean delivery.

We found a higher rate of some complications than has been reported from other institutions. For example, the rate of placenta previa with accreta in our series (7.0/1000 patients with prior cesarean sections) was

Table I. Characteristics of study patients

Case	*Age (yr)*	*Gestational age (wk)*	*Obstetric history*	*Labor*	*Complication*	*Surgical therapy*
1	33	34	7 NSD; 1 vertical CS, 1 rupture at 20 weeks	Elective CS	Rupture; maternal death; PE	TAH
2	31	40	LT CS, 5 AB, 1 Molar	PROM; TOL; oxytocin; epidural; pain and fetal bradycardia; clinical abruptio placentae	Rupture	CS; repair; BTL
3	25	36	NSD, PT LT CS	PROM, pain and fetal tachycardia; clinical abruptio placentae; no TOL	Rupture	CS; repair
4	21	38	PT LT CS, RPT LT CS	Prolonged latent phase; TOL; bleeding, pain, and mass	Rupture; extruded fetus	Exp. lap; repair
5	22	33	2 LT CS	IUFD; failed oxytocin induction; clinical abruptio placentae	Rupture; extruded; fetal death	TAH
6	29	30	4 NSD, PT CS Unk.	Pain; anemia; no TOL	Rupture; extruded fetus; fetal death	TAH
7	23	35	LT CS	Severe preeclampsia; PG gel ripening; TOL; oxytocin induction; epidural; arrest of dilatation; pain	Rupture, extruded cord	CS; repair
8	22	35	CS Unk., 2 AB	Severe preeclampsia; oxytocin induction; TOL; epidural; late decelerations; clinical abruptio placentae; pain	Rupture	CS; repair
9	28	36	PT LT CS	Premature labor; TOL; VBAC	Rupture	Exp. lap.; repair
10	27	37	2 LT CS	Elective CS	Placenta previa-increta	TAH
11	23	35	4 CS Unk.	Elective CS	Placenta previa-accreta	Int. iliac art. lig.; TAH
12	27	37	LT CS, 2 AB	Elective CS	Placenta previa-increta	TAH
13	29	34	2 LT CS, 2 ectopic	Bleeding; CS	Placenta previa-perceta; maternal death	TAH; int. iliac art. lig.
14	35	36	4 CS Unk., 2 AB	Elective CS	Placenta previa-accreta	TAH
15	32	22	LT CS	Bleeding; hypotension	Placenta previa	D&E; int. iliac art. lig.; TAH
16	38	39	2 CS Unk., 2 AB, 1 ectopic	Elective CS	Placenta previa	Uterine and ovarian art. ligations
17	28	35	2 CS Unk., 1 PT CS	Bleeding; CS	Placenta previa	TAH

AB, Abortion; *BTL,* bilateral tubal ligation; *CS,* cesarean section; *D&E,* dilation and extraction; *Exp. lap,* exploratory laparotomy; *Int. iliac art. lig.,* internal iliac artery ligation; *IUFD,* intrauterine fetal death; *LT,* low transverse; *NICU,* neonatal intensive care unit; *NSD,* normal spontaneous delivery; *PROM,* premature rupture of membranes; *PG,* prostaglandin; *PE,* pulmonary embolus; *PT,* preterm; *RPT,* repeat; *TAH,* total abdominal hysterectomy; *TOL,* trial of labor; *Unk.,* unknown scar; *VBAC,* vaginal birth after cesarean.

*Packed red blood cells.

Table II. Categories of serious complications among the 17 study patients

Complication	*No.*	*No./1000 pregnancies with previous cesarean*
Death	5	7.0
Maternal	2	2.8
Fetal	3	4.2
Hemorrhage	11	15.5
Uterine rupture	9	12.7

twice that found by Clark et al.[7] Our rate of uterine rupture was 14.2/1000 for women during a trial of labor and 10.5/1000 for those delivered without a trial of labor. Previous studies have reported uterine rupture rates of 0.9 to 8.2/1000 laboring women and 1.9 to 4.7/1000 in those who did not labor.[2-4, 8-13] The variance between these results and our own could relate to differences in the characteristics of study samples (our hospital treats a largely black and Latin Ameri-

Transfusion*	Birth weight	Apgar scores (1 min/5 min)	NICU days
3	2500	8/9	0
6	3865	8/8	0
0	1850	4/8	21
0	2810	3/5	5
10	1485	0/0	—
10	1615	0/0	—
2	2700	3/4	4
3	1870	1/3	14
2	2620	8/8	2
4	3005	7/8	0
5	2510	8/9	60
5	2900	7/8	0
19	2200	5/7	20
5	3005	8/9	0
13	—	0/0	—
2	3140	8/9	0
5	2240	7/7	10

can low-socioeconomic population), to the well-known problem of complete case finding in retrospective studies,[14] to a currently more liberal attitude toward allowing a trial of labor, or to the rigor with which complications have been defined in various studies. We are confident that we identified all cases at our institution that were delivered during the study period and met the study criteria.

We considered that our approach to labor, which involves the careful use of oxytocin for induction or stimulation of labor based on the same criteria we use in women without a cesarean section scar,[15] might have led to a high rate of uterine rupture. The fact that our uterine rupture frequency among women before labor was also higher than that of many previous reports makes it more likely that other factors are operative. Although data from several institutions support the safety of oxytocin stimulation during trials of labor,[16, 17] definitive information with regard to this issue is lacking.

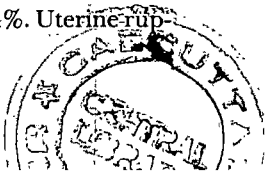
Of the patients who had uterine rupture during labor, it is of interest that the three women who had epidural anesthesia nevertheless had pain attributable to the rupture. Two cases of rupture had what might be considered prolonged arrest disorders and showed no response to 4 and 10 hours of oxytocin administration, respectively, before delivery. These cases suggest that arrest disorders might indicate or predispose a patient to uterine rupture, or that perhaps a trial of labor should be discontinued if there is not a prompt response to uterine stimulation. One rupture occurred during sedation for prolonged latent phase labor, and another was noted during an evaluation of postpartum hemorrhage after a normal labor and delivery. Thus rupture can occur with relatively mild uterine activity, can be asymptomatic during labor, and does not preclude normal dilatation and descent. These conclusions must be tempered by the fact that we could not always determine precisely when during the course of parturition some ruptures occurred.

Interestingly, four instances of uterine rupture were initially diagnosed as abruptio placentae with fetal distress. In view of this, we think that clinical signs of abruptio placentae in a woman with a previous cesarean scar should always raise concerns about the possibility of uterine rupture.

The significance of our finding that four of the nine uterine ruptures in our series occurred in patients whose previous cesarean section was performed preterm is uncertain. It could imply that cesarean section in a uterus before term confers increased risk of subsequent rupture, perhaps because the lower uterine segment is less likely to have been well developed.

The striking frequency of placenta previa and placenta accreta in this series is consistent with the previously observed predilection of the placenta to implant in the vicinity of the uterine scar and for invasion of the myometrium by trophoblast to occur.[6] These cases and the uterine ruptures often required urgent and extensive surgery, including hysterectomy and ligation of major pelvic arteries. Physicians caring for patients with cesarean section scars should be comfortable performing these procedures and handling their potential complications.

In summary, we found the frequency of very serious complications in a series of pregnancies undertaken after previous cesarean section to be 2.4%. Uterine rup-



ture and placenta previa or various degrees of placenta accreta were the major contributors to mortality and serious morbidity. Trials of labor in women with previous low transverse cesarean sections contributed to 56% of the uterine ruptures, but several occurred before labor and would thus not necessarily have been prevented by elective repeat cesarean section. The information provided by this study may be useful in assessing risks of pregnancy with a previous cesarean. More importantly, the observed frequency and nature of complications in subsequent pregnancies, particularly in women with more than one prior cesarean delivery, emphasizes the importance of performing cesarean section only when the benefits to be accrued outweigh potential risks.

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Antibiotic therapy in preterm premature rupture of membranes: A randomized, prospective, double-blind trial

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The use of antibiotics in the management of preterm, premature rupture of membranes remains controversial. By use of a prospective randomized double-blind design we investigated the maternal-fetal benefits associated with antibiotic therapy in 85 women with premature rupture of membranes at 34 weeks' estimated gestational age. In the treatment group 40 patients received intravenous mezlocillin for 48 hours followed by oral ampicillin until delivery. In the control group 45 patients received intravenous and oral placebo. Patients who received antibiotics had chorioamnionitis and endometritis less frequently than the control group ($p < 0.01$ and $p < 0.05$). Pathologic examination of the placentas showed a lower incidence of chorioamnionitis in the treatment group ($p < 0.05$). The period from premature rupture of membranes to delivery (latency) was prolonged with antibiotics ($p < 0.05$) and resulted in significant weight gain in the infants in the antibiotic group ($p < 0.0001$). These infants also had higher 1- and 5-minute Apgar scores. Clinically suspected sepsis, respiratory distress syndrome, intraventricular hemorrhage, perinatal death rate, and prolonged hospitalization (>30 days) were also increased in the control group. (AM J OBSTET GYNECOL 1990;163:743-7.)

Key words: Antiobiotics, premature rupture of membranes, preterm

Preterm, premature rupture of the fetal membranes is associated with significant perinatal morbidity and mortality. Women with preterm premature rupture of membranes often have chorioamnionitis and postpartum endometritis-myometritis. The infants frequently have respiratory distress syndrome (RDS), sepsis, intraventricular hemmorrhage, or necrotizing enterocolitis. An infant with any of these complications must be admitted to a neonatal intensive care unit. The costs of caring for these infants are high with prolonged hospitalization. At the University Medical Center in Jacksonville 3% of all deliveries are associated with premature rupture of membranes at <34 weeks' gestation. The perinatal mortality rate as a result of preterm premature rupture of membranes at University Medical Center in 1987 was 129/1000 live births. Neonatal sepsis, RDS, and intraventricular hemorrhage were frequent complications.[1]

Previous publications suggest that a large proportion of cases with premature rupture of membranes are the result of occult infections.[2-6] *Neisseria gonorrhoeae* and group B streptococcal colonization of the cervix have been associated with an increased risk of premature rupture of membranes. An occult infection of the cervix may initiate a sequence of biochemical pathways leading to premature rupture of membranes and subsequent labor.[4] Because of this risk of occult infection use of tocolytics and steroids in premature rupture of membranes is discouraged.[7, 8] A few studies have focused attention on the use of antibiotics in premature rupture of membranes.[9-13] However, only two studies could be found that used a prospective, double-blind, randomized design.[12, 13] Both showed no benefits to the infants when antiobiotics were used. Two recent prospective randomized studies examined ampicillin prophylaxis in preterm premature rupture of the membranes.[14, 15] These showed benefits to the infants when antibiotics were used. However, these were not double-blind studies, and some patients underwent tocolysis, some received steroids, whereas others had both or neither modes of therapy.

The purpose of our study was to investigate whether antibiotics administered to women with preterm premature rupture of membranes (<34 weeks) would decrease maternal or perinatal morbidity and mortality, or both.

Material and methods

The study population included all women who came to the University Medical Center–Jacksonville, Florida labor and delivery suite with premature rupture of the membranes from 20 to 34 weeks gestational age. The

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study was performed with approval of the University Medical Center Institutional Review Board. Only mothers with singleton gestations between 20 and 34 weeks' gestational age with premature rupture of membranes who signed an informed consent were included. Premature rupture of membranes was confirmed by sterile speculum examination for pooling, ferning, and Nitrazine paper testing. Patients were excluded from the study if they had an allergy to penicillin, were taking antibiotics at the time of premature rupture of membranes, had fever >100.4° F, had signs and symptoms of chorioamnionitis, were in active labor (defined as three or more contractions per 10-minute period for 1 hour, or if they presented with cervical dilation >3 cm confirmed at the time of sterile speculum exam. Fetal indications for exclusion were the presence of fetal distress, defined as repetitive late deceleration or sustained bradycardia, and congenital abnormality noted on ultrasonographic examination.

After the patient was included in the study a medical history was obtained and physical examination was performed. The history included the mother's age, race, gravidity, parity, estimated gestational age by last menstrual period, date and time of premature rupture of membranes, presence of contractions, abdominal pain, fever, presence of any maternal illness or pregnancy-related complications, use of medications, and allergies. A complete physical examination including abdominal palpation for uterine tenderness and fundal height measurement and sterile speculum examination with fern and Nitrazine paper testing was performed. If fluid was present at the vaginal vault, it was collected for fetal lung maturity evaluation. The cervix was inspected for dilatation and cultures for gonorrhea and streptococcus were obtained. Digital vaginal examination was not allowed. The estimated gestational age and fetal weight, presentation of the fetus, and the presence or absence of oligohydramnios were documented by ultrasonography. A biophysical profile was obtained including a nonstress test. Laboratory studies included a complete blood cell count with differential, serum electrolytes, rubella, serologic tests for syphilis, blood type, and antibody screen, urinalysis, and urine culture and sensitivity. Randomization was accomplished by a table generated by consecutive coin toss; the randomization schedule was kept in the pharmacy and was unavailable to the clinicians.

After 8 hours of monitoring if there was no evidence of labor, chorioamnionitis, or fetal distress as previously defined the patient was transferred to the antepartum unit on strict bed rest; vital signs and fetal heart tones were recorded every 2 hours. Physical examination, a biophysical profile, and complete blood count were completed daily. If any evidence of labor or chorioamnionitis developed the patient was transported to the labor and delivery unit for management. No tocolytic agents or steroids were given. If labor continued the patient was allowed to deliver spontaneously. Chorioamnionitis was diagnosed by a temperature >100.4° in combination with either uterine tenderness, fetal tachycardia, foul-smelling vaginal discharge, or a white blood cell count >20,000/mm^3. In the presence of chorioamnionitis, antibiotics were not given if delivery was imminent. However, if delivery did not appear to be imminent, intravenous gentamicin and ampicillin were started as well as oxytocin induction or augmentation when appropriate. At that time the study drug was discontinued.

In those patients in whom labor or chorioamnionitis did not develop, evidence of fetal distress by external auscultation, biophysical profile, or nonstress testing became an indication for immediate transport to the labor and delivery unit for management. Fetal distress was diagnosed by persistent late decelerations, prolonged fetal bradycardia, or a score of <4 on biophysical profile. Delivery was expedited by appropriate methods in accordance with standard obstetric practice for persistent fetal distress.

If the initial cervical cultures for B-hemolytic streptococci or gonorrhea were positive, the study drug was discontinued and the patient received intravenous ampicillin or other appropriate antibiotic coverage for penicillin-resistant gonorrhea. However, the patient was not removed from the group to which she had been randomized and was included in the statistical analysis at the completion of the study. When fetal pulmonary maturity was suspected, a repeat amniotic fluid sample from the vagina or by amniocentesis was sent for phosphatidylglycerol determination or the lecithin/sphingomyelin ratio. Evidence of pulmonary maturity was an indication for induction of labor in fetuses >34 weeks' gestation.

Spontaneous delivery was allowed for vertex presentations. Malpresentations were delivered by cesarean section. At delivery the infant's age was estimated according to the Dubowitz scoring system, arterial cord gas studies were obtained, and cultures were obtained from the placenta 1 cm within the fetal and maternal surfaces. The fresh placenta was sent for histologic examination for funisitis, amnionitis, and chorioamnionitis.[16] At delivery the study drug was discontinued and the mother was transported to the postpartum unit and discharged home on the second postpartum day. Endometritis-myometritis was diagnosed by a temperature of 100.4° F on at least two occasions after the first 24 hours after delivery associated with uterine tenderness and no other focus of infection. If endometritis-myometritis was diagnosed the mother received gentamicin and clindamycin.

After delivery the infants were admitted to the nurs-

ery. The neonatologists were unaware of which treatment the mother had received. Blood cultures using antibiotic resin and a complete blood count were collected on admission. At the discretion of the neonatologist other studies included cerebrospinal fluid examination, chest x-ray film, and urinalysis. All infants then received intravenous ampicillin and amikacin. The neonatologist evaluated the infant between 12 and 48 hours of age and recorded the presence or absence of RDS, sepsis, pneumonia, or other complications that may have been present. RDS was diagnosed by respiratory distress necessitating oxygen therapy and a chest x-ray film consistent with hyaline membrane disease. Clinical sepsis was diagnosed by the neonatologist when the infant presented with hypothermia, hypotension, hyporeflexia, tachypnea, neutropenia, or leukocytosis with a left shift. Positive blood cultures were not considered essential for a diagnosis of sepsis, because the mother may have received antibiotics before delivery. Pneumonia was diagnosed by chest x-ray films and clinical examination. Intraventricular hemorrhage was diagnosed and graded by ultrasonographic examination. If cultures obtained from the infant were negative and there was no clinical suspicion of sepsis, use of antibiotics was discontinued at 72 hours. Infant antibiotic treatment was continued if the neonatologist suspected sepsis on the basis of the above criteria.

In a study performed at University Medical Center in 1987 the incidence of RDS in premature rupture of membranes before 34 weeks' estimated gestational age was 27%.[1] To show a 50% reduction in the incidence of RDS in the antibiotic group at the 95% confidence level, 60 patients were needed in each phase of the study, for a total of 120 participants. However, the study was stopped at 85 patients because of time constraints and the diminution of resources.

After the 85 patients had been delivered, statistical analysis was performed, using Student t test, χ^2 test, and Kaplan-Meier estimation when appropriate. After the analysis the study code was broken to determine the groups that received antibiotics or placebo.

Results

Eighty-five patients were randomized into a placebo group ($n=45$) and a treatment group ($n=40$). There were no significant differences between the two groups with respect to maternal age, race, gestational age by dates, gestational age by ultrasonography, estimated fetal weight by ultrasonography, prenatal care, and hours of premature rupture of membranes (Table I). There were no maternal deaths in either group.

Table II describes the infectious morbidity of the women in the study. Twenty-one patients in the placebo group also had positive cultures. Six of these patients had both gonorrhea and group B streptococcal organisms. Five had gonorrhea and 10 had group B streptococci. Of these 21 patients four were treated before delivery and chorioamnionitis did not develop. Chorioamnionitis developed in four patients during labor and these patients were treated. The other thirteen were not treated until after delivery.

Table I. Demographic data

	Placebo	*Antibiotic*
No.	45	40
Maternal age (yr)	22.3 ± 1.0	23.6 ± 1:0
White	9 (20%)	10 (25%)
Black	36 (80%)	30 (75%)
Gestational age by dates (wk)	30.3 ± 0.5	29.5 ± 0.7
Gestational age by ultrasonography (wk)	29.6 ± 0.6	29.2 ± 0.6
Estimated fetal weight by ultrasonography (gm)	1412 ± 610	1423 ± 651
Prenatal care	20 (44%)	18 (45%)
Hours*	5.2 ± 1.0	6.1 ± 1.3

p = NS.
*Hours of premature rupture of membranes on admission.

Table II. Maternal morbidity

	Placebo	*Antibiotics*	*p Value*
Endometritis-myometritis	15 (33%)	5 (12%)	<0.05
Chorioamnionitis	16 (35%)	3 (7%)	<0.01
Chorioamnionitis of placenta*	19 (75%)	12 (46%)	<0.05

*Histopathologic diagnosis.

The culture results were not available until 48 to 72 hours after collection. For this reason some patients were delivered before the diagnosis of the positive culture was available.

In the treatment group five patients had positive cultures for both gonorrhea and group B streptococci, three had gonorrhea only, and six had only group B streptococci organisms. Eleven of these 14 patients were delivered before the diagnosis was made. Chorioamnionitis developed in three and they were treated during labor, and three were diagnosed and treated before chorioamnionitis or labor developed. All these patients were retained in the study in their respective groups for the purpose of statistical analysis.

Chorioamnionitis, as defined above, was diagnosed in 16 patients in the placebo group compared with three patients in the antibiotic group. Endometritis-myometritis was found in 33% of the placebo group in comparison with 12% of the antibiotic group.

The interval from premature rupture of membranes to delivery (latency period) was significantly longer in the treated group (Table III). The mean latency period

Table III. Latency period*

Duration (days)	*Placebo*	*Antibiotics*	*p Value*
≥7	8 (18%)	18 (45%)	<0.01
≤2	6 (13%)	1 (2%)	NS†

*Period from randomization to delivery.
†$p = 0.06$.

Table IV. Indications and mode of delivery

	Placebo	*Antibiotic*
Spontaneous labor	23	26
Induced because of chorioamnionitis*	17	6
Induced because of suspected lung maturity	3	4
Fetal distress	2	2
Cesarean section	6	9
Forceps-vacuum	5	3
Spontaneous vaginal delivery	34	28

*$p < 0.05$.

was 8.25 days in the treatment group compared with 3.82 days in the placebo group. Seventy-five percent of the placebo group were delivered by day 3 after admission into the study. Conversely, 75% of the treatment group were not delivered until day 9 of admission into the study.

The indications for delivery were similar in the two groups (Table IV). The only significant difference was in the number of labors that were induced or augmented because of the suspicion of chorioamnionitis ($p < 0.05$).

The neonatal outcomes are listed in Table V. The infants born to mothers in the antibiotic group remained in utero longer and had significantly greater weight gain from time of premature rupture of membranes to delivery.

Table VI presents the neonatal morbidity data. Two infants in the placebo group had blood cultures positive for group B β-hemolytic streptococci within the first 48 hours of life. Clinical sepsis, as previously defined, was significantly more frequent in the placebo group ($p < 0.05$). A trend was present showing an increase in RDS in the placebo group. Intraventricular hemorrhage and hospital stay were significantly lower in the antibiotic group ($p < 0.05$).

Comment

Antibiotics were used in this study based on the assumption that premature rupture of membranes is initiated by an occult infection. If no treatment is started, this presumed infection may progress to frank chorioamnionitis and spontaneous labor. The purpose of our study was to arrest and cure any infection already present, not to prevent an infection. For this purpose mezlocillin, a broad-spectrum antibiotic that has proved to be effective when administered as a single-agent therapy for chorioamnionitis and endometritis-myometritis, was chosen.[17] Mezlocillin crosses the placenta and is found in cord blood and amniotic fluid at therapeutic levels, yet has no adverse effects on perinatal or postnatal development.

Patients with positive cultures were not removed from the study. Because it often takes longer than 48 hours to obtain a culture result, many patients with preterm premature rupture of membranes are delivered before the culture result is available. Antibiotic therapy may benefit such patients. Because patients with positive cultures represent a subset of all patients with premature rupture of membranes, they should be included in a study that investigates the benefits of initiating antibiotic therapy at the onset of premature rupture of membranes. As noted, four patients in the placebo group were diagnosed with positive cultures before the onset of labor or chorioamnionitis and were treated appropriately. It would be unethical to withhold antibiotics in such a situation. However, they remained

Table V. Neonatal outcome

	Placebo	*Antibiotic*	*p Value*
Number of infants	45	40	
Stillbirth	1	0	
Neonatal death	3	3	
Birth weight (gm)	1587 ± 592	1897 ± 600	<0.05
Weight gain (gm)	175 ± 46	456 ± 80	<0.001
Dubowitz (wk)	30.9 ± 0.7	32.4 ± 0.6	<0.05
Apgar score			
1 min	5.4 ± 0.5	6.9 ± 0.4	<0.05
5 min	7.9 ± 0.4	8.2 ± 0.3	NS
Cord arterial pH	7.25 ± 0.01	7.26 ± 0.01	NS
SGA	3 (6%)	3 (7%)	NS

SGA, Small for gestational age.

Table VI. Neonatal morbidity

	Placebo	*Antibiotics*	*p Value*
Positive blood cultures	2 (4%)	0	NS
Clinical sepsis	11 (24%)	3 (7%)	<0.05
Respiratory distress	11 (24%)	6 (15%)	NS
IVH	14 (31%)	5 (12%)	<0.05
NEC	3 (6%)	2 (5%)	NS
NICU (stay in days)	11.8 ± 21.9	12.3 ± 35.9	NS
Hospital stay >30 days	17 (38%)	7 (18%)	<0.05
Duration intravenous antibiotics (days)	4.7 ± 3.5	3.8 ± 2.5	NS

IVH, Intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit.

in the placebo group and their data were included in the statistical analysis at the end of the study. Three patients in the treatment group received appropriate treatment for positive cervical cultures before labor or chorioamnionitis developed.

The use of tocolysis and steroids was intentionally omitted so that the impact of the variable under study (antibiotics) would be elucidated. It was thought that once the role for antibiotics in premature rupture of membranes is established, then any advantage of adding tocolysis, or steroids, or both could be investigated at a later date. In this study mothers and infants with preterm premature rupture of membranes treated with antibiotics experienced better outcomes as measured by several parameters. The incidence of chorioamnionitis and endometritis-myometritis significantly decreased. Treated infants remained in utero twice as long and experienced three times the weight gain than that of the placebo group. Infants from the treatment group had significantly higher 1-minute Apgar scores and significantly decreased frequencies of intraventricular hemorrhage and clinically suspected sepsis. There was a trend toward less RDS. Furthermore, the treatment group infants had a decreased chance of prolonged hospitalization (>30 days).

Although the numbers do not permit adequate evaluation, it was noted that no difference in the perinatal death rate occurred between the two groups. The combined perinatal death rate was 70.6/1000 live births. In 1987 at the same institution before the initiation of this study, the perinatal death rate in cases of premature rupture of membranes before 34 weeks' gestational age was 129/1000 live births.[1] Perhaps the initiation of this study helped to decrease the premature rupture of membranes perinatal death rate in 1988. This study required close supervision of the mothers and meticulous antenatal testing of fetal well-being on a daily basis. The stringent supervision of patients with premature rupture of membranes required by the study design may have helped to decrease the perinatal death rate in both groups.

We conclude that the assumption of infection in preterm premature rupture of membranes in some patients is correct, and that since we are unable to clearly define which patients have occult infection, that antibiotic therapy appears to be justified. We found significant improvements in maternal and fetal outcomes. We did not discover any adverse effects from administering the antibiotics. However, it is understood that complications such as anaphylaxis or superinfection with opportunistic organisms can occur. The fact that we did not observe these complications could be explained by the small sample size.

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Effect of tocolytic agents on fetal umbilical velocimetry

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In this prospective study, we sought to examine the changes in umbilical vascular resistance induced by tocolytic therapy. Umbilical artery velocimetry was performed in 46 patients with preterm labor before tocolysis and at 1 hour and 24 hours after tocolysis was initiated. Raw systolic/diastolic ratios were corrected for concomitant changes in fetal heart rate. Thirty patients received subcutaneous terbutaline and 16 were treated with intravenous magnesium. Systolic/diastolic ratios decreased in patients treated with terbutaline. This decline persisted after correction for increases in fetal heart rate. No significant changes in systolic/diastolic ratios were seen in patients treated with magnesium. We conclude that terbutaline may affect umbilical vascular resistance. Possible clinical implications of these findings are discussed. (AM J OBSTET GYNECOL 1990;163:748-50.)

Key words: Tocolytic, Doppler, umbilical velocimetry, terbutaline, magnesium

β-Sympathomimetic tocolytic drugs have profound effects on the maternal and fetal cardiovascular systems. Beta receptors are known to be present in the umbilical and uterine vasculature[1] and β-sympathomimetic tocolytics are known to cross the placenta.[2] It is possible that the vasodilatory action of β-sympathomimetics may affect vascular resistance in the umbilical circuit.

The recent development of fetal Doppler studies provides a noninvasive means of assessing umbilical vascular resistance. Brar et al.[3] used Doppler velocimetry to demonstrate a decline in umbilical vascular resistance in patients treated with ritodrine. However, these authors believed that increases in fetal heart rate may have confounded these results.

The purpose of this study was to assess the effect of terbutaline on umbilical vascular resistance as measured by systolic/diastolic ratio while controlling for the effect of an increase in fetal heart rate.

Material and methods

In this prospective study 46 patients who were seen in the labor and delivery suite with preterm labor were enrolled. Preterm labor was defined as gestational age between 25 and 34 weeks, and uterine contractions persisting after hydration, with cervical change. Patients with ruptured membranes, fetal congenital anomalies, previous tocolytic therapy, or complications associated with uteroplacental insufficiency were excluded. The choice of tocolytic agent was made by the individual patient's physician.

Thirty patients received terbutaline subcutaneously 0.25 mg every hour for 3 doses, every 3 hours for 8 doses, then 2.5 to 5 mg orally every 3 to 6 hours. Magnesium sulfate was given intravenously as a 4 gm loading dose followed by 2 to 3 gm/hr by infusion pump. After 8 to 12 hours of successful tocolysis with magnesium sulfate, patients were switched to oral magnesium oxide therapy, 200 to 400 mg every 4 hours.

A continuous-wave Doppler velocimeter (Angioscan III, Ultrasonix, Inc. North Yonkers, N.Y.) with a 4 MHz transducer was used to obtain all systolic/diastolic ratios. Patients were examined in the recumbent position with 15 to 30 degrees of lateral uterine displacement. Readings were taken between contractions in the absence of fetal breathing or fetal body movement. All studies were performed by one of the authors. The Doppler probe was positioned on the abdomen to obtain the best quality umbilical artery signals as recognized by the characteristic waveform and umbilical vein flow in the opposite direction. Peak systolic and lowest diastolic frequency shifts were measured with electronic calipers. Systolic/diastolic ratios were then calculated with five waveforms averaged to obtain each reading. Fetal heart rates were calculated by measuring the distance between waveform peaks with electronic calipers. Six patients in each group were initially studied before tocolysis was initiated, then at 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, and 48 hours after tocolysis was begun. This was done to estimate appropriate time intervals for study. On the basis of these preliminary results we studied the remaining

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Table I. Raw umbilical artery systolic/diastolic ratios

	Baseline	*1 hr*	*24 hr*	*Time effect*
Terbutaline	$n = 30$	$n = 30$	$n = 26$	
Mean ± SD	3.13 ± 0.80*	2.73 ± 0.56*†	2.47 ± 0.48†	$p < 0.001$
Magnesium	$n = 16$	$n = 16$	$n = 16$	
Mean ± SD	2.91 ± 0.66	3.04 ± 0.53	2.85 ± 0.51	p = NS
Between groups	p = NS	$p = 0.03$	$p = 0.004$	

*$p = 0.004$.
†$p = 0.04$.

Table II. Fetal heart rates

	Baseline	*1 hr*	*24 hr*	*Time effect*
Terbutaline	$n = 30$	$n = 30$	$n = 26$	
Mean ± SD	136 ± 10.1*	140 ± 11.7*†	144 ± 9.9†	$p < 0.001$
Magnesium	$n = 16$	$n = 16$	$n = 16$	
Mean ± SD	140 ± 13.3	136 ± 11.5	136 ± 10.2	p = NS
Between groups	p = NS	p = NS	$p < 0.001$	

*p = NS.
†$p = 0.01$.

Table III. Corrected umbilical artery systolic/diastolic ratios

	Baseline	*1 hr*	*24 hr*	*Time effect*
Terbutaline	$n = 30$	$n = 30$	$n = 26$	
Mean ± SD	3.07 ± 0.79*	2.73 ± 0.51*†	2.54 ± 0.45†	$p < 0.001$
Magnesium	$n = 16$	$n = 16$	$n = 16$	
Mean ± SD	2.92 ± 0.57	2.98 ± 0.50	2.80 ± 0.50	p = NS
Between groups	p = NS	$p = 0.05$	$p < 0.05$	

*$p = 0.009$.
†p = NS.

patients before tocolysis and at 1 hour and 24 hours after tocolysis was initiated.

Systolic/diastolic ratio data were analyzed in both raw form and after correction for fetal heart rate according to the method suggested by Mires et al.[4] For these systolic/diastolic ratio data and for fetal heart rate, analysis of variance for repeated measures was used to assess the effects of group and time. Duncan's new multiple range test was then performed for differences between individual means. The Statistical Analysis Systems statistical package was used for all analyses.

Results

Thirty patients received terbutaline and 16 received magnesium. The average gestational age was 30.8 ± 2.6 weeks and did not differ between groups. Four patients in the terbutaline group failed tocolysis after 1 hour. Thus 26 patients in the terbutaline group were examined at 24 hours. All patients in the magnesium group had labor successfully arrested for at least 24 hours.

Patients treated with terbutaline demonstrated a significant decrease in systolic/diastolic ratios ($p < 0.001$) (Table I). The majority of the decline in systolic/diastolic ratio occurred within 1 hour after the first dose of terbutaline. These differences were significant between baseline and 1-hour measurements, as well as between 1-hour and 24-hour measurements. The terbutaline group also exhibited a concomitant increase in fetal heart rate ($p < 0.001$) (Table II). The overall decline in systolic/diastolic ratio was still significant after correction for changes in fetal heart rate (Table III); however, the difference between the 1-hour and 24-hour measurements was no longer significant. The magnesium group exhibited no change in systolic/diastolic ratios (Tables I and III) or fetal heart rate (Table II). There were significant differences between the two groups for both raw and corrected systolic/diastolic ratios at 1 hour and 24 hours.

Comment

Our study shows a decline in umbilical artery systolic/diastolic ratios associated with use of terbutaline. This decline persisted after correction for fetal heart rate, which is the major known confounding variable. We found no similar change in the systolic/diastolic ratios of fetuses exposed to magnesium.

Brar et al.[3] recently found a significant decrease in

the uterine and umbilical artery systolic/diastolic ratios in patients treated with ritodrine for preterm labor. There was also a concomitant increase in the maternal and fetal heart rates, which the authors thought might have changed the systolic/diastolic ratios. They found no change in systolic/diastolic ratios or heart rates in patients treated with magnesium sulfate. In our study we corrected for the effects of fetal heart rate changes and confirmed that this decline in umbilical artery systolic/diastolic ratio is present in patients exposed to β-sympathomimetic.

Many patients and fetuses are exposed to tocolytic agents during pregnancy. Maternal side effects from these agents are well known and are sometimes serious. Conversely, fetal effects are less often considered. β-Sympathomimetic tocolytics have been associated with fetal cardiac dysrythmia, heart failure, myocardial ischemia, ventricular septal hypertrophy, and neonatal death.[5]

The possibility that β-sympathomimetic agents may affect fetal vascular resistance is physiologically sound. This study and that of Brar et al.[3] offer scientific data as confirmation. It may seem that vasodilation should promote better blood flow and oxygen delivery. However, Parisi and Walsh[6] have shown that vasodilation in the fetus may actually decrease placental blood flow by shunting blood to other vascular beds. It is possible that a decrease in vascular resistance caused by β-sympathomimetic tocolytics could be harmful to the fetus. Additionally, consideration also should be given to a patient's current drug therapy when interpreting diagnostic umbilical velocimetry measurements.

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Does the umbilical artery systolic/diastolic ratio reflect flow or acidosis?

An umbilical artery Doppler study of fetal sheep

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We studied four fetal sheep at 114 to 139 days' gestation to evaluate the effect of acute placental embolization on placental perfusion, fetal oxygenation and acid-base status, and the umbilical artery systolic/diastolic ratio. Studies were performed after maternal anesthesia was induced in an acute model, with serial umbilical artery embolizations performed at 20 to 30 minute intervals. Fetal umbilical flow, systolic/diastolic ratio, and arterial blood gas levels were followed up. One animal maintained a normal systolic/diastolic ratio despite a 50% drop in flow after the first injection and pH of 6.91, and died after the second injection. The remaining three animals showed significantly decreased flow after the third injection ($p < 0.02$), with no change in the systolic/diastolic ratio. The systolic/diastolic ratio increased significantly after the fourth injection ($p < 0.05$) when flow had dropped even further. Corresponding decreases in Po_2 and pH did not achieve statistical significance. The magnitude of all changes increased with subsequent embolizations. We conclude that in this model significant reductions in flow result in small increases in the systolic/diastolic ratio and that greater magnitude changes in the systolic/diastolic ratio appear only with severely diminished flow and Po_2, when acidosis develops. (Am J Obstet Gynecol 1990;163:751-6.)

Key words: Umbilical blood flow, Doppler ultrasonography, fetal flow, fetal sheep

The umbilical artery Doppler waveform has been proposed as a means to determine placental flow, function, and resistance.[1-4] Many growth-retarded fetuses show diminished end-diastolic frequency shifts.[5-10] In vitro, Doppler-derived flow measurements can be shown to correlate well with true volume flow.[11] The placental circulation is a complex system, and because of the tortuous nature of the umbilical arteries, as well as the broad spectra of the flow-velocity waveforms obtained from them, calculation of absolute flow in the umbilical arterial circulation is not yet feasible. This study was undertaken as part of an effort to match physiologic data in the catheterized fetal sheep to Doppler flow-velocity waveforms. The hypothesis to be tested was that acute reductions in umbilical arterial flow by placental embolization to increase placental resistance would lead to corresponding changes in the Doppler waveforms, as measured by the systolic/diastolic (S/D) ratio.

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Material and methods

We studied four mixed breed fetal sheep at 114 to 139 days' gestation. After an overnight fast, the animals were brought to the operating suite and general endotracheal anesthesia was induced. Anesthesia was maintained with 2% halothane in oxygen. Laparotomy was performed and the pregnant horn was identified and opened. Through a left flank incision, the fetal common umbilical artery was identified, and a perivascular flow probe (Transonics Systems, Ithaca, N.Y.) was placed around it. Catheters were placed in the fetal femoral artery and vein. The femoral arterial catheter was advanced into the distal aorta to a point above the level of the common umbilical artery. After the fetus was replaced and the uterus was closed, the middle uterine artery feeding the pregnant horn was identified, and another perivascular flow probe was placed around it. The abdomen was then closed.

Blood gas data were obtained from an ABL2 blood gas machine (Radiometer, Copenhagen). Flow information was continuously collected on an IBM personal

computer with a commercially available data acquisition program (CODAS, Dataq Instruments, Akron, Ohio). Resistance was computed from the flow and arterial pressure information stored in this data base.

Abdominal ultrasonography was performed with an Advanced Technology Laboratories UltraMark 4 system (ADR Ultrasound, Bothell, Wash.), and the umbilical cord was identified. Doppler flow-velocity waveforms were obtained with a 3 MHz mechanical sector transducer and were recorded on videotape, with still images additionally obtained at the time fetal blood gas levels were collected, generally just before and 5 minutes after each embolic challenge. S/D ratios were measured whenever possible from the internal calipers of the Advanced Technology Laboratories machine, although some were not measured during the actual experiment. For those data, the videotape audio signal was fed through a Multigon 500A spectrum analyzer (Multigon, Mt. Vernon, N.Y.) and the S/D ratio was measured from that instrument's internal calipers. The S/D ratio was measured by placement of calipers at the peak systolic and end-diastolic frequencies of consecutive waves.

Average flow information was computed as the mean for 15-second intervals. The corresponding Doppler signals were taken from the same 15-second interval. At least three waves were analyzed, and the mean was calculated.

The experimental protocol consisted of baseline measurements of flow, Doppler waveforms, and fetal arterial blood gas levels after a stabilization period of at least 30 minutes. This was followed by an injection into the common umbilical artery of 10 ml dextran. Sequential embolizations were then performed by injection of 1.6 to 3.2×10^7 carbonized latex microspheres 15 μm in diameter through the catheter placed at the level of the common umbilical artery. Injections were given every 20 minutes, with an arterial blood gas measurement obtained 5 minutes later. The Doppler, resistance, and flow information were extracted for the same time as that of the blood gas sample.

Data were analyzed by use of paired Student t tests with statistical significance accepted at $p < 0.05$. S/D ratios were logarithmically transformed to impose a linear distribution.

Results

One of the sheep did not adequately recover a normal pH after surgery and remained at 6.91 through the baseline and control injection periods. The fetus died after the second embolic injection. It is interesting to note that the umbilical flow dropped by 50% after the first injection with no change in S/D ratio (Fig. 1).

The remaining three sheep were studied through six embolizations, receiving a mean total of 1.28×10^8 microspheres. Fig. 2 shows the sequential means of the S/D ratios, flows, and resistance values. The mean initial flow was 368 ml/min, the mean initial resistance was 209 dynes cm^{-2} ml min^{-1}, and the mean initial S/D ratio was 1.91. All were unchanged after the dextran control injection.

The first embolization dropped the flow to 354 ml/min, and the resistance rose to 220 dynes cm^{-2} ml min^{-1}. The S/D ratio was 1.8, unchanged from baseline. The second embolic injection decreased mean flow still further to 321 ml/min, whereas resistance rose to 252 dynes cm^{-2} ml min^{-1}. Mean S/D was 1.97.

The S/D ratio rose moderately after the third injection to 2.27, whereas the mean flow had dropped to 305 ml/min, and resistance rose to 252 dynes cm^{-2} ml min^{-1}. The flow was significantly reduced from baseline ($p < 0.02$), whereas the S/D ratio was not significantly elevated ($p = 0.27$). The resistance showed a trend, that was not significant ($p = 0.07$).

The fourth injection further compromised flow to 278 ml/min ($p < 0.001$ relative to baseline values), with resistance rising to 290 dynes cm^{-2} ml min^{-1} (still not achieving statistical significance). The S/D ratio rose to 2.55 ($p < 0.05$). The fifth and sixth injections had continuing effects on all three variables.

The mean initial pH was 7.16, which dropped minimally to 7.14 after the third embolization. After the fourth injection the mean pH was 7.11, not reaching significance ($p < 0.09$). The fifth injection lowered the pH still further to 7.05 ($p < 0.06$), whereas it reached 6.98 after the sixth injection ($p < 0.005$) (Fig. 3).

A look at each sheep individually further shows the pattern of responses to the embolizations. Fig. 4 shows the composite information for the three sheep that survived the entire protocol, comparing the S/D ratio with the umbilical flow data. The break points for the S/D ratios appear to be lagging behind the drops in flow.

In Fig. 5 the umbilical S/D ratio is compared with the fetal arterial pH. The break point more closely approximates that of the S/D ratio than was apparent from the flows.

Comment

The analysis of Doppler flow-velocity waveforms from the umbilical artery has been suggested to be beneficial in the identification of the growth-retarded fetus.[6, 7] Although whether it is better than ultrasonographic biometry remains in question, it may be a useful adjunct.[12] It has also been implied to be helpful to distinguish the true-positive from the false-positive contraction stress test, suggesting that fetal asphyxia or acidosis may influence the waveform shape.[13]

In this study we acutely stressed the fetoplacental circulation by repeatedly embolizing the common umbilical artery. After several challenges the umbilical flow began to drop, and was significantly reduced before there was any change in the S/D ratio. After one to two further injections we saw an increase in the S/D

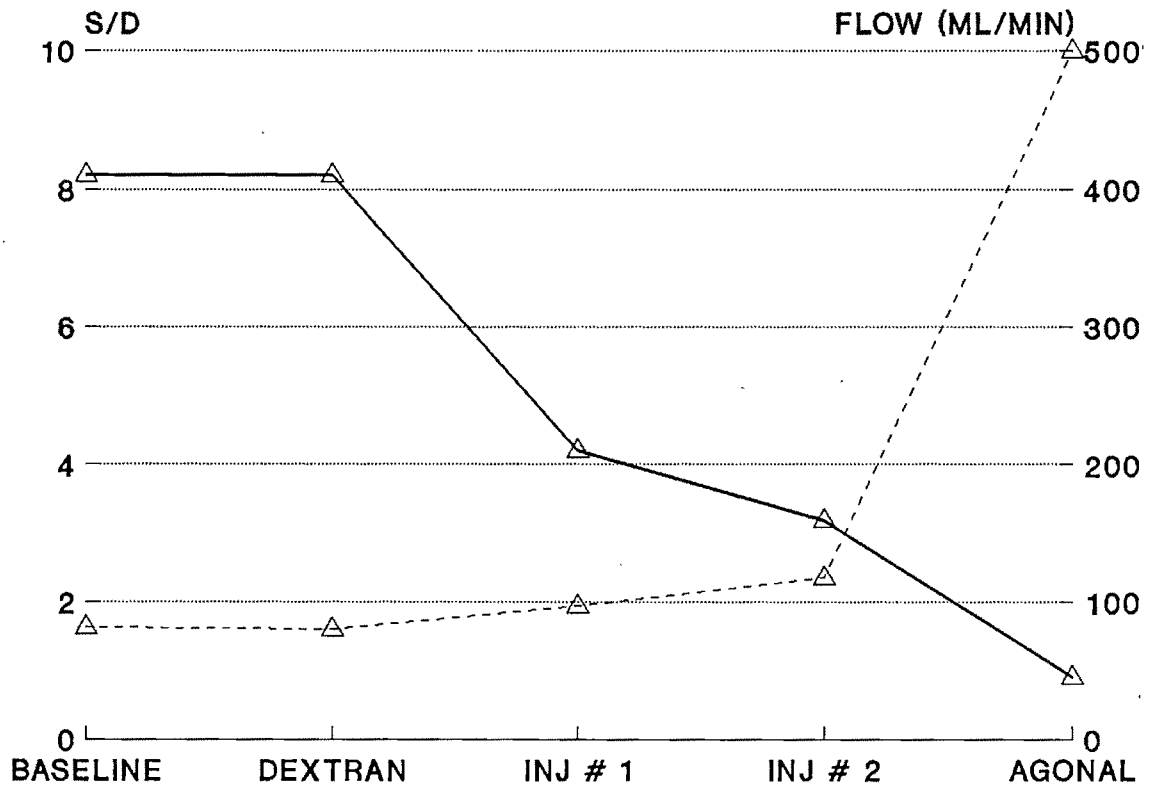


Fig. 1. Sheep MF 64. Sequential umbilical artery flow and S/D ratios over time. Flow (*solid line*) shown with scale on right; S/D (*dashed line*) with scale on left. Last value obtained 9 minutes after second injection, just before fetal death.

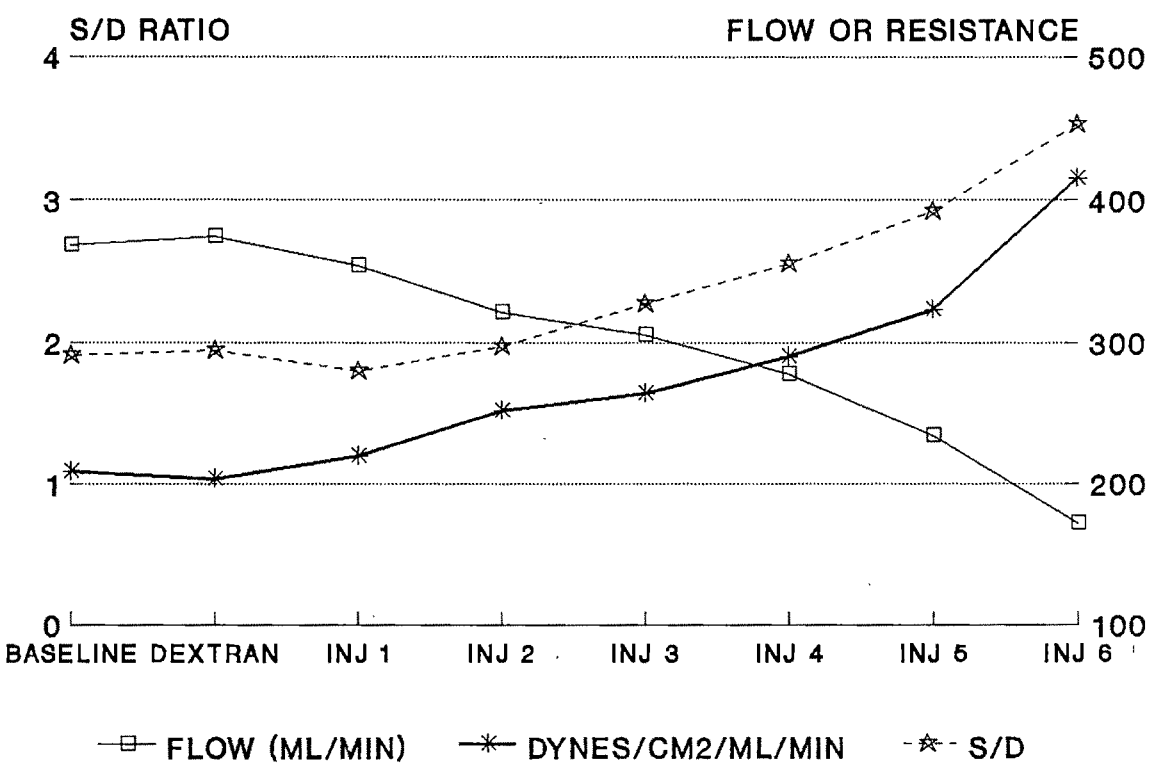


Fig. 2. Mean flow, resitance and S/D ratios for three sheep surviving entire protocol. Flow (milliliters per minute, *light line*) and resistance (dynes cm^{-2} ml min^{-1}, *heavy line*) with scale on right; S/D ratio (*dashed line*) with scale on left.

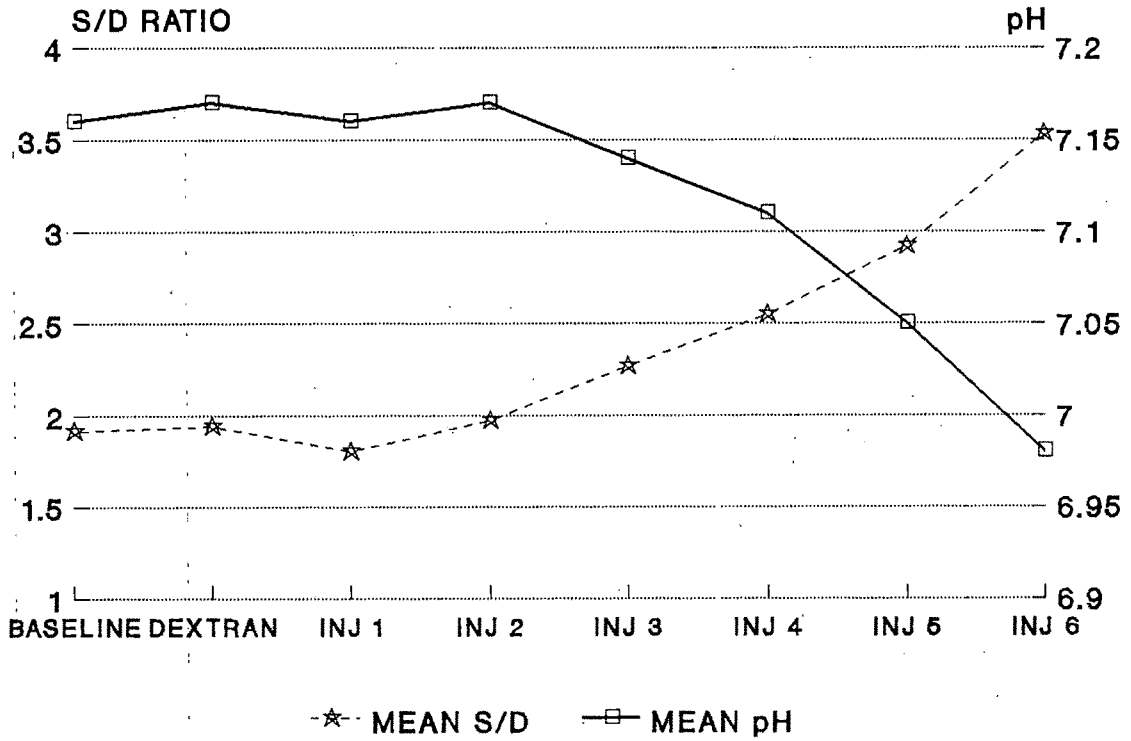


Fig. 3. Mean S/D ratio and umbilical arterial pH over time for three sheep surviving entire protocol. S/D ratio (*dashed line*) with scale line on left; pH (*heavy line*) with scale on right.

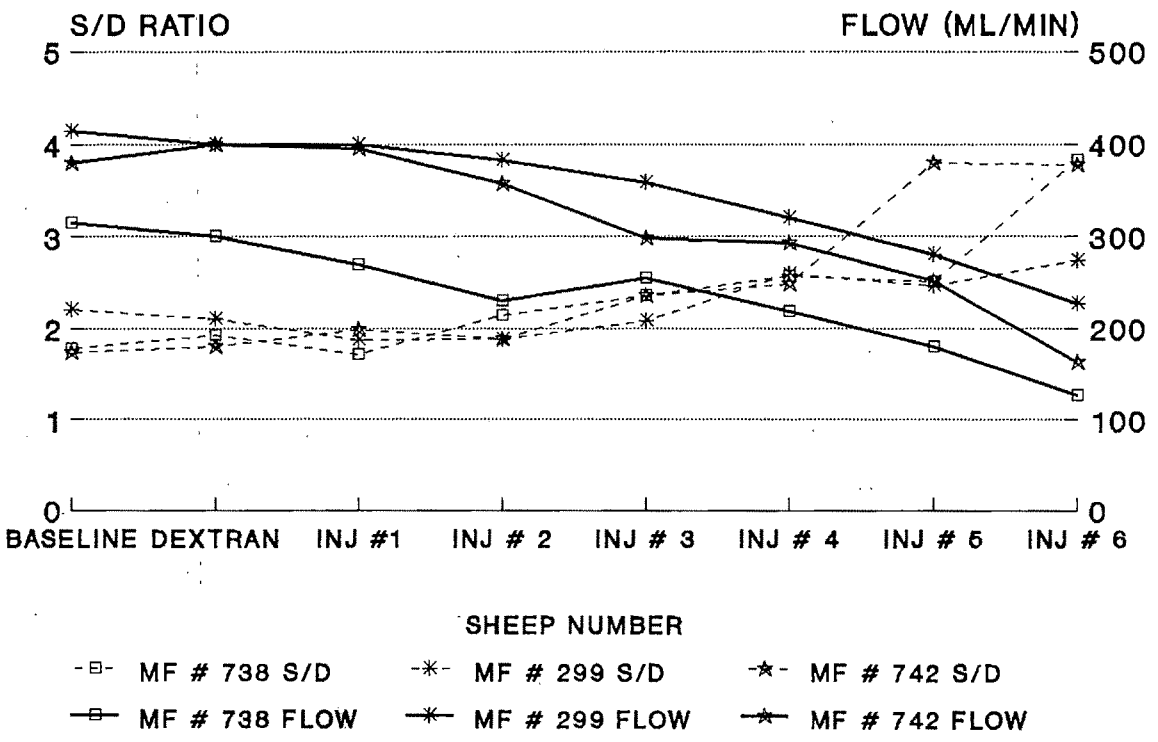


Fig. 4. Composite of three surviving sheep showing flow and S/D ratios over time. For each, flow shown (*heavy line*) with scale on right; S/D ratio shown (*dashed line*) with scale on left. Sheep 738, *box*; sheep 299, *asterisk*; sheep 742, *star*.

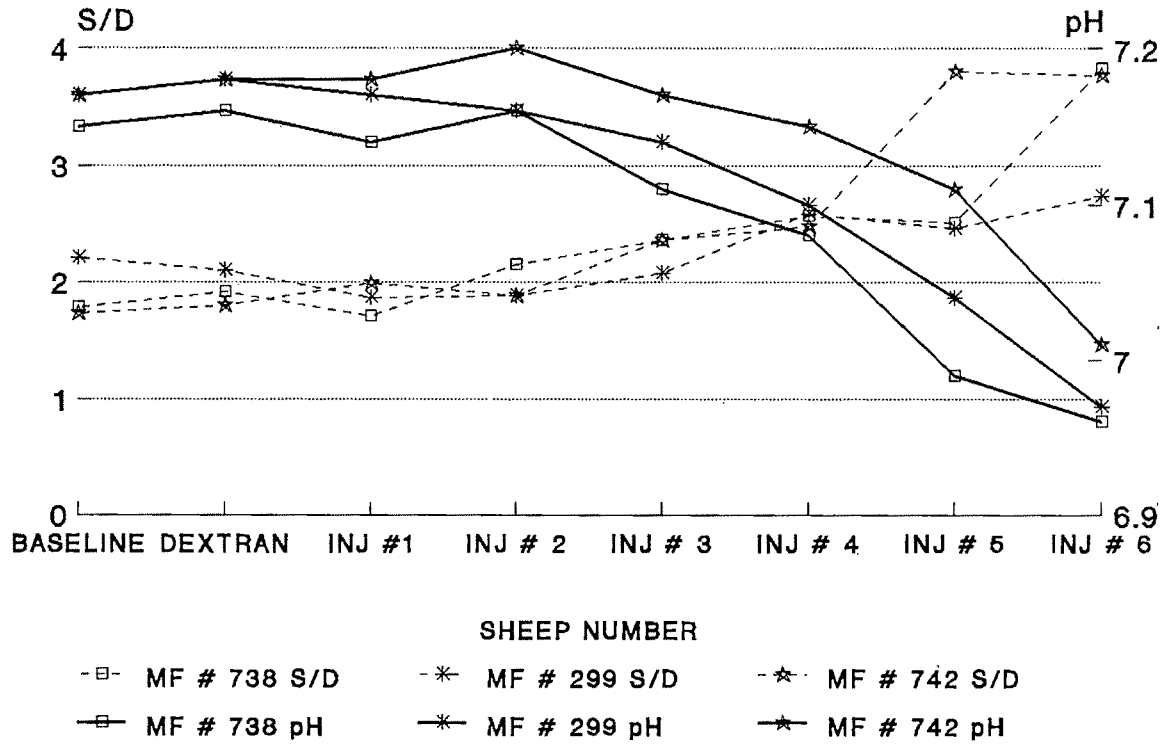


Fig. 5. Composite of three surviving sheep showing pH and S/D ratios over time. Legend same as in Fig. 4.

ratio, approximately at the same time that the pH began to drop.

The most dramatic change we observed was in one fetus that remained acidotic after surgery, with pH 6.91. The umbilical artery S/D ratio was normal compared with the other lambs in this study and compared with Trudinger's standards[14] (1.62 versus Trudinger's mean 2.2). The first injection reduced umbilical flow by 50% with no change in S/D, whereas the fetus died shortly after the second injection. At 5 minutes after the second injection flow had dropped to 40% of baseline and the S/D rose to 2.35. Shortly after that the flow dropped to about 10% of baseline, at which point diastolic flow disappeared.

In the remaining three sheep, baseline S/D ratios were in the normal range as previously reported by Trudinger[14] and by Newnham.[15] Whereas the pH values appear low, the initial pH values were all within 2 SEMs as reported by Trudinger. Initial umbilical flows, and Po_2s were also within 2 SEMs reported by Trudinger. Thus the acute stresses of surgery did not appear to have altered these physiologic parameters at the start of the embolization series.

We observed significant drops in flow in all the sheep before obvious changes were apparent in the S/D ratio. The calculated placental resistance rose with each embolic injection. The reason for the lag in change of the S/D ratio after the change in flow is unclear. It may be a result of the time allowed for observation in this experimental design. But it may also reflect a true lack of sensitivity of the ratio to early, but nonetheless significant, reductions in flow. For example, an increase in spectral broadening or change in waveform shape may occur as flow initially drops. We did not attempt such measurements in the current study for a number of reasons. The simple S/D ratio will not change with either altered spectral broadening or changes in wave shape. The resistance index will also not be altered by either of these. The pulsatility index should reflect altered waveform shapes, but provides no information about spectral broadening. Because of the limitations of the equipment used for this set of experiments, we were unable to measure the pulsatility index. Spectral broadening is also not measurable by currently available equipment.

The ability of umbilical artery Doppler waveforms to change early in the course of adverse fetoplacental changes is critical to our understanding of the appropriate applications of this technology. For example, we previously observed on the lack of sensitivity of the S/D ratio to acute asphyxial insults in the fetus (unpublished observation).

In conclusion, we have found that the umbilical artery S/D ratio lagged behind true umbilical flow in alterations induced by acute placental embolization. We also showed that normal umbilical artery S/D ratios can

be found even in the presence of severely compromised flow and critical fetal acidosis. These preliminary data suggest that careful evaluation of chronic models of fetal and placental damage will be necessary to understand whether umbilical artery Doppler can be used to identify early chronic growth restriction in the fetus.

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Infection and labor

VI. Prevalence, microbiology, and clinical significance of intraamniotic infection in twin gestations with preterm labor

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The purpose of this study was to establish the prevalence, microbiology, and outcome of microbial invasion of the amniotic cavity in twin gestation presenting with preterm labor and intact membranes. Amniocenteses were performed on both sacs of 46 women with twin gestations, preterm labor, and intact membranes. Indigo carmine was injected to ensure sampling of both amniotic sacs. Amniotic fluid was cultured for aerobic and anaerobic bacteria, *Mycoplasma hominis*, and *Ureaplasma urealyticum*. A positive amniotic fluid culture of at least one sac was noted in 10.8% (5/46) of patients admitted in preterm labor and in 11.9% (5/42) of women delivered of preterm neonates. Of the five patients with microbial invasion of the amniotic cavity, three had microorganisms isolated from both sacs. The presenting sac was involved in all cases, supporting an ascending route for microbial invasion of the amniotic cavity in twin gestation. Polymicrobial infection was found in three of the eight amniotic sacs with positive cultures. In two cases different organisms were isolated from each sac. All patients with positive amniotic fluid cultures were delivered of preterm infants within 48 hours of amniocentesis. Patients with positive amniotic fluid cultures presented with preterm labor at an earlier gestational age and with more advanced cervical dilatation than did women with negative amniotic fluid cultures. Clinical evidence of chorioamnionitis subsequently developed in two of five women with positive amniotic fluid cultures. The interval between amniocentesis and delivery was shorter in women with positive amniotic fluid cultures than in women with negative amniotic fluid cultures (median: 3.5 vs 168 hours, $p < 0.0001$). Infants born to women with microbial invasion of the amniotic cavity had a lower median birth weight and a higher incidence of respiratory distress syndrome than those born to women with negative amniotic fluid cultures (birth weight: 1085 vs 1975 gm, $p = 0.024$; respiratory distress syndrome: 37.5% vs 8.3%, $p = 0.04$). (Am J Obstet Gynecol 1990;163:757-61.)

Key words: Intraamniotic infection, twin gestation, chorioamnionitis, prematurity, preterm labor, parturition, labor

Although multiple gestation is an important risk factor for preterm labor and delivery,[1] the mechanisms responsible for preterm birth in this setting are poorly defined. Recently, the association between subclinical intrauterine infection and preterm labor has been recognized in singleton gestations (reviewed in reference 2). The contribution of intrauterine infection to the etiology of preterm labor in multiple gestation has not been established. The purpose of this study was to determine the prevalence of microbial invasion of the amniotic cavity in the setting of twin gestations.

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Material and methods

Patient population. Patients admitted to Yale–New Haven Hospital with the diagnosis of twin gestation and preterm labor with intact membranes were offered amniocentesis for evaluation of the microbiologic status of the amniotic cavity. Patients were enrolled between Aug. 29, 1985, and Aug. 28, 1989. Preterm labor was defined as the presence of regular uterine contractions with a frequency of at least two every 10 minutes and documented cervical change in patients with a gestational age of < 34 weeks. Nitrazine, pooling, and ferning tests were performed in every case during a sterile speculum examination to exclude patients with rupture of membranes. Ritodrine, terbutaline, or magnesium sulfate was administered intravenously for tocolysis. Failure of tocolysis was diagnosed when cervical

dilatation progressed beyond 5 cm or delivery occurred.

Retrieval of amniotic fluid. Amniotic fluid was retrieved by transabdmonial amniocentesis performed under ultrasonographic guidance. Indigo carmine was injected after fluid was retrieved from the first sac to ensure sampling of both amniotic cavities.

Microbiologic studies. Amniotic fluid was transported to the laboratory in a capped plastic syringe immediately after collection. These conditions precluded air contact with the specimen. Plating occurred within 30 minutes of collection in all cases. Amniotic fluid was cultured for aerobic and anaerobic bacteria, as well as for *Mycoplasma* species, with techniques previously described in detail.[3] The results of the Gram stain examinations of amniotic fluid were shared with the clinicians. Patients with negative Gram stain examinations for bacteria were given tocolytic drugs. Patients with positive Gram stain examinations for bacteria were given parenteral antibiotics and allowed to labor. A positive Gram stain for bacteria was an indication for discontinuing tocolysis.

Criteria for the diagnosis of intraamniotic infection, neonatal sepsis, and respiratory distress syndrome. Intraamniotic infection was diagnosed by the presence of a positive amniotic fluid culture.[4] Clinical chorioamnionitis was defined according to the criteria proposed by Gibbs et al.[5] Neonatal sepsis was diagnosed by the presence of a positive culture of blood, urine, or cerebrospinal fluid. Respiratory distress syndrome (RDS) was defined as chest retractions, expiratory grunting, and a decrease in air entry that occurred shortly after birth and persisted for at least 6 hours, accompanied by a reticulogranular pattern in the chest film and without any evident cause of the respiratory distress.

Statistical analysis. Comparisons were performed with contingency tables and Fisher's exact test or χ^2 as appropriate. Amniocentesis to delivery interval and cervical dilatation between patients with positive and negative amniotic fluid cultures were compared with a Mann-Whitney U test.

Results

Amniotic fluid was retrieved from both sacs in 46 patients. A positive amniotic fluid culture of at least one sac was noted in 10.8% (5/46) of patients admitted with preterm labor. Of the 42 patients who went on to deliver preterm neonates, 11.9% (5/42) had a positive amniotic fluid culture. All five patients with a positive amniotic fluid culture had a preterm delivery. Of the five patients with positive amniotic fluid cultures, three had microorganisms isolated from both sacs. Table I displays the microbial isolates and quantitative microbiologic results for patients with a positive amniotic fluid culture.

Of the eight amniotic sacs with positive cultures, three had multiple microbial isolates. The Gram stain of amniotic fluid was positive for microorganisms in only one of eight colonized fluids. The presenting sac was involved in every case. There were no cases in which the nonpresenting sac was colonized without involvement of the presenting sac. In three patients the same microorganism was isloated from both sacs. The colony count and the number of microbial isolates were higher in the presenting than in the nonpresenting sac. The placentas of all twins with a positive amniotic fluid culture were dichorionic and diamniotic except for one case (monochorionic and diamniotic, case 3 in Table I). Clinical chorioamnionitis developed in two of the five women with positive amniotic fluid cultures and in none of the 42 patients with negative amniotic fluid cultures ($p = 0.009$). There were no cases of neonatal sepsis.

Table II displays gestational age and cervical dilatation on admission and the interval between amniocentesis and delivery, according to amniotic fluid culture results. Patients with positive amniotic fluid cultures presented with a more advanced cervical dilatation and progressed more rapidly to delivery than women with negative amniotic fluid cultures.

All patients with positive amniotic fluid cultures were delivered of preterm infants within 48 hours of amniocentesis. Fig. 1 displays the utilization of and response to tocolysis of all patients in this study. Of those with negative amniotic fluid cultures, four were delivered of term infants (>37 weeks). None of the neonates had confirmed sepsis. Infants born to women with positive amniotic fluid cultures had lower mean birth weights and a higher incidence of RDS than those born to women with negative amniotic fluid cultures (birth weight: median, 1085 gm; range, 540 to 2300 gm vs median, 1816 gm; (320 gm to 2480 gm); $p = 0.024$ (Mann-Whitney test); RDS: 37.5% (3/8) vs 8.3% (7/84); $p = 0.04$ (Fisher's exact test), respectively.

Comment

The association between intrauterine infection and preterm labor and delivery in singleton gestation has been the subject of intense investigation (reviewed in reference 2). The mean prevalence of positive amniotic fluid cultures in patients presenting with preterm labor and intact membranes is 13.6% (range, 0% to 25%).[6-17] Furthermore, in a recent study 21.6% of women who presented with preterm labor and intact membranes and went on to deliver a preterm neonate had a positive amniotic fluid culture.[4]

Although multiple gestation is a known risk factor for preterm delivery, the etiology of preterm birth in this setting is poorly understood. The traditional ex-

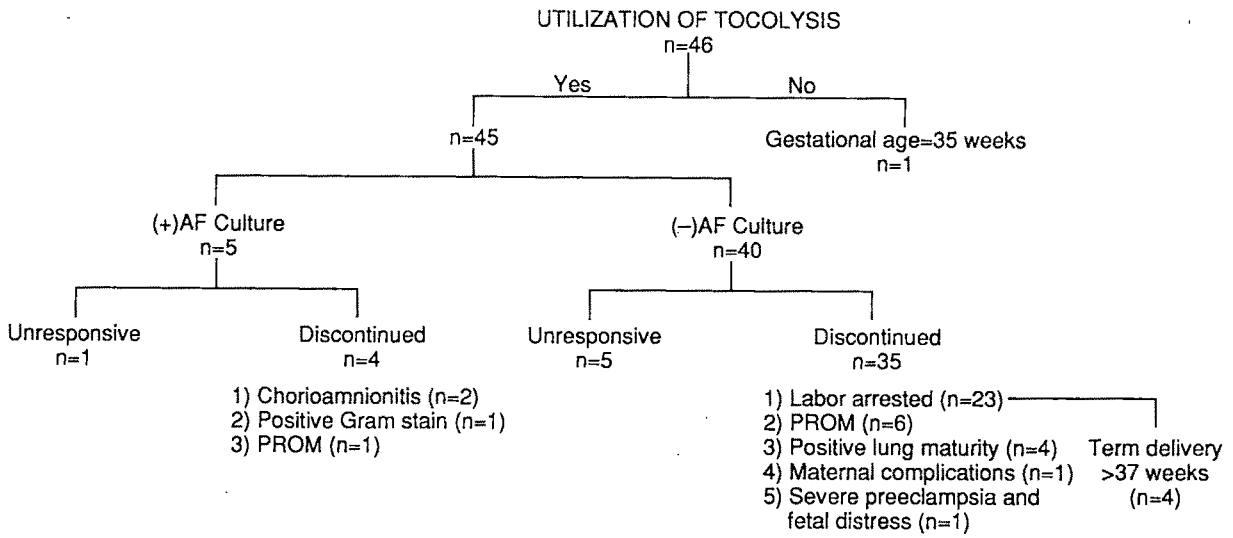


Fig.1. Utilization of tocolysis, response, and indication for discontinuation in patients with twin gestation and preterm labor

Table I. Quantitative microbiology and clinical chorioamnionitis of patients with microbial invasion of the amniotic cavity

Twins	*Culture results*	*Colony count (CFU/ml)*	*Placentation*	*Clinical chorioamnionitis*
A_1	*Fusobacterium nucleatum*	30,000	Dichorionic Diamniotic	Yes
B_1	*Fusobacterium nucleatum*	1,000		
A_2	*Ureaplasma urealyticum* *Peptostreptococcus*	39,000	Dichorionic Diamniotic	No
B_2	*Peptostreptococcus*	100		
A_3	*Fusobacterium nucleatum* *Ureaplasma urealyticum* *Mycoplasma hominis*	100,000	Monochorionic Diamniotic	Yes
B_3	*Fusobacterium nucleatum*	1,000		
A_4	*Ureaplasma urealyticum*		Dichorionic Diamniotic	No
B_4	–			
A_5	Mixed aerobic gram-positive bacteria of three varieties	100	Dichorionic Diamniotic	No
B_5	–			

CFU/ml, Colony forming units per milliliter.

planation for the higher rate of preterm delivery in these gestations has been that uterine overdistention causes premature activation of the mechanisms responsible for the initiation of labor.[18] However, it is also possible that the premature cervical effacement and dilatation that occurs in multiple gestations favors an ascending infection and this, in turn, leads to preterm labor or preterm premature rupture of membranes (PROM).[19]

Our data indicate that microbial invasion of the amniotic cavity occurs in 11.9% of twin gestations presenting with preterm labor and delivering a preterm neonate (<37 weeks). This finding is in contrast to the 21.6% of positive amniotic fluid cultures observed in singleton gestations with preterm labor and delivery.[4] These data suggest that intraamniotic infection is a possible cause of preterm labor and delivery in twin gestation. However, the results of this study do not support the hypothesis that intraamniotic infection is responsible for the excessive rate of preterm delivery observed in twin gestations.

Intrauterine infection usually follows an ascending pathway from the lower genital tract. The observations made in this study support this view. First, in all cases of microbial invasion of the amniotic cavity, the presenting sac was involved. Second, when the same microorganism was found in both sacs, the inoculum size was larger in the presenting sac. Finally, no microbial

Table II. Clinical characteristics of patients with and without microbial invasion of the amniotic cavity

	Positive amniotic fluid culture	*Negative amniotic fluid culture*	*p Value*
Gestational age (wk) at presentation (mean ± SD)	29.2 ± 4.2	30.1 ± 4.2	NS
Cervical dilatation (cm) (mean and range)	4 (2-5)	2 (0-5)	0.047
Amniocentesis to delivery interval (hr) (mean and range)	3.5 (3-41)	168 (10–6 wk)	0.001

invasion was detected in the nonpresenting sac without involvement of the presenting sac.

The pathway of infection of the nonpresenting sac is not known. Infection of the second sac may be the result of further spread of decidual infection that has already involved the presenting sac or may be caused by transmembranous invasion from the presenting sac or by hematogenous spread. It is unclear whether the type of placentation (monochorionic or dichorionic) has a role in limiting transmembranous spread of infection. The spatial orientation of the sacs may have a role in determining the risk of infection of the second sac. If both sacs have sections adjacent to the cervix, the likelihood of infection is expected to be greater than if only one sac fills the entire lower uterine segment. The isolation of *Fusobacterium* species in two of our patients is of particular interest because these microorganisms are rarely a component of the normal vaginal flora. Vaginal cultures for these microorganisms were not performed in our patients, and thus we cannot comment on the source of this infection.

The contribution of intraamniotic infection to the morbidity and mortality of the preterm neonate is another issue that requires investigation. Neonates born to women with positive amniotic fluid cultures in singleton gestations are delivered at an earlier gestational age and have an excess of neonatal infectious morbidity, lower Apgar scores, and lower birth weights than those neonates born to women with negative amniotic fluid cultures.[4] In the current study neonates born to women with positive amniotic fluid cultures had a higher incidence of respiratory distress and lower mean birth weights than those born to women with negative amniotic fluid cultures. The extent to which respiratory distress is caused by aspiration of infected amniotic fluid and pneumonitis cannot be determined. The difficulties in the differential diagnosis between RDS and congenital pneumonia have been previously recognized.[20] Further studies are required to determine whether the excess incidence of respiratory complications in newborns born to women with positive amniotic fluid cultures is due to prematurity or to in utero microbial exposure.

The second twin generally has a greater incidence of complications.[21] Discordant intraamniotic infection may play a role in the differential morbidity and survival of twins. It might be argued that an intraamniotic infection in the presenting sac stimulates maturity in the presenting fetus while the second twin is not exposed to this stressing factor(s). This view may also be relevant to twin gestation complicated with preterm PROM.

It is impossible from this type of study to determine whether microbial invasion of the amniotic cavity is the cause of preterm labor or merely its consequence. Indeed, cervical dilatation as a result of labor could allow microorganisms from the lower genital tract to traverse intact membranes and gain access to the amniotic cavity. Alternatively, an ascending infection may signal the onset of labor. If intraamniotic infection is causally related to the initiation of parturition, our data would seem to suggest that infection of one sac is enough to trigger the onset of labor. Twin gestation offers a unique and naturally occurring model for the study of the mechanisms involved in the control of human parturition.

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Superiority of the four-quadrant sum over the single-deepest-pocket technique in ultrasonographic identification of abnormal amniotic fluid volumes

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Ultrasonographic estimation of amniotic fluid volume is an important adjunct to assessment of fetal well-being. However, no single method has emerged as most predictive. Many ultrasonographers use subjective or single-pocket guidelines in evaluation of amniotic fluid volume. We therefore assessed the ability of a maximum-vertical-pocket technique to identify patients with abnormal volumes of amniotic fluid. A total of 1168 patients was studied. Oligohydramnios (n = 76) was defined as an amniotic fluid index <5th percentile for gestational age (70 to 98 mm). Hydramnios (n = 51) was defined when the amniotic fluid index was >95th percentile (185 to 249 mm). The ability of the maximum-vertical-pocket technique to identify cases with oligohydramnios by amniotic fluid index was poor: sensitivity was 42% and positive predictive value was 51%. Fifty-eight percent of cases with oligohydramnios by amniotic fluid index had "normal" values according to the single-pocket technique. The correlation coefficient between amniotic fluid index and maximum vertical pocket was 0.51, R^2 = 24%. The correlation between the maximum vertical pocket and amniotic fluid index was somewhat better in cases of polyhydramnios (r = 0.79, R^2 = 62%), but the sensitivity, positive predictive value, and false-negative rates were high as in oligohydramnios. These data suggest that the maximum-vertical-pocket technique has adequate specificity but is a poor screening tool. The results demonstrate that use of gestation-specific norms for the amniotic fluid index identifies abnormal amniotic fluid volumes more efficiently than the single-pocket technique. (AM J OBSTET GYNECOL 1990;163:762-7.)

Key words: Oligohydramnios, amniotic fluid, polyhydramnios

Ultrasonographic estimation of amniotic fluid volume is an important adjunct to assessment of fetal well-being.[1, 2] However, no single method has emerged as most predictive. Subjective scales have been proposed,[3, 4] but these lack reproducibility. Somewhat arbitrarily defined "maximum-vertical-pocket depths" of amniotic fluid visualized on ultrasonographic scans have been used as a relative indication of amniotic fluid volume. Manning et al.[1] demonstrated that absence of a single pocket of amniotic fluid 1 cm in depth was associated with increased risk of fetal distress and perinatal mortality. Chamberlain et al.[5] used a "2 cm rule" to define marginal amniotic fluid (3% of 7582 high-risk patients). Intrauterine growth retardation and perinatal death were increased in these pregnancies. Similarly, a single pocket exceeding 8 cm (3% of their high-risk population) was predictive of increased rates of macrosomia.[6] However, Hoddick et al.[7] subsequently demonstrated that the "1 cm rule" has poor sensitivity in prediction of growth retardation. Bottoms et al.[8] noted that the maximum vertical pocket varied significantly during gestation and asserted that application of a single depth criterion was no better than subjective grading of amniotic fluid volume. To expand the sampling field, Phelan et at.[9] summed vertical fluid pockets in four quadrants of the uterus. Values of the amniotic fluid index <5 cm were predictive of high rates of meconium staining, fetal distress, and cesarean section.[10]

Most of the aforementioned studies have attempted to correlate one-dimensional scales of amniotic fluid depth to fetal outcome, yet none has established the ability of these schemes to predict accurately the amniotic fluid volume present. Recently we have demonstrated in the pregnant sheep that the amniotic fluid index has a close linear relationship to actual amniotic fluid volume (Volume = $-152+(4.2 \cdot$ amniotic fluid index), r = 0.94). In this setting, the amniotic fluid index was able to quantitate volume with 88% accuracy.[11] Moreover, our studies of normal amniotic fluid index

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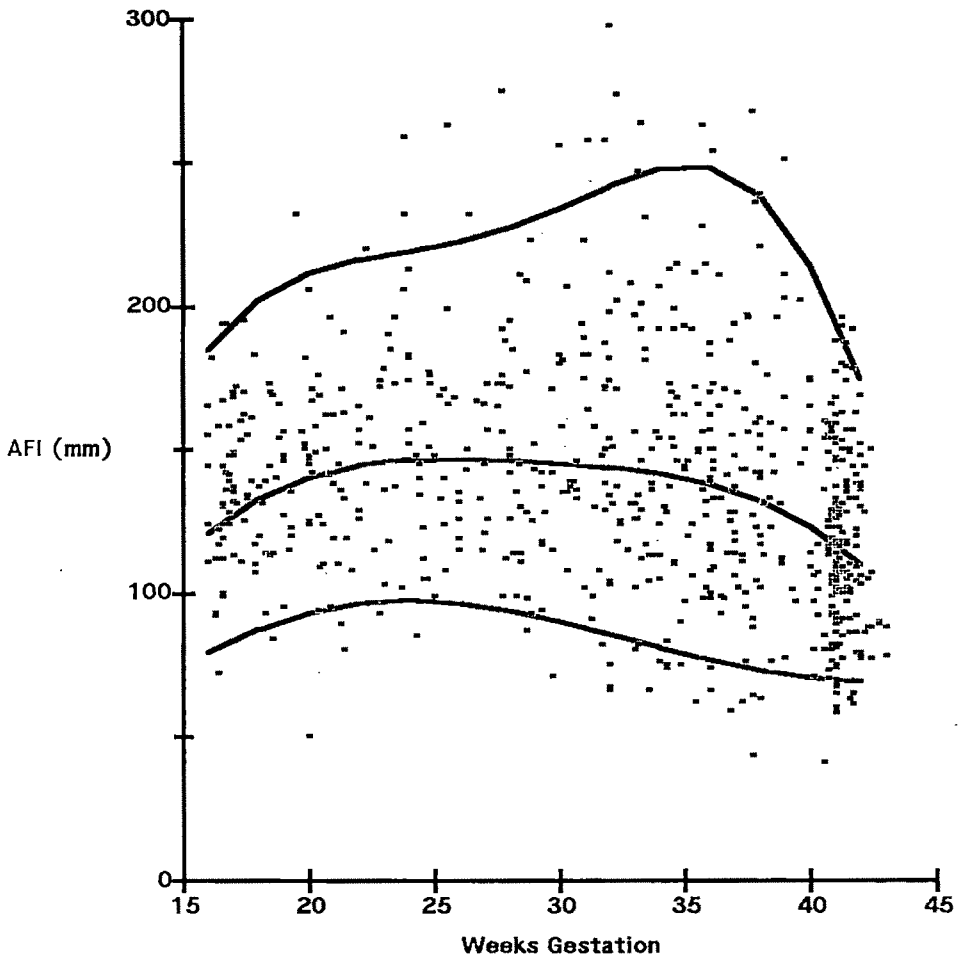


Fig. 1. Amniotic fluid index *(AFI)* data points from normal patients plotted against gestational week. *Upper, middle,* and *lower lines* represent 95th, 50th, and 5th percentiles, respectively.

values in human pregnancy[12] have yielded a curve that is remarkably similar to that generated from indicator-dilution studies.[13]

The purpose of this investigation therefore was to compare the efficiency of single-value maximum-vertical-pocket cutoff values (2, 8 cm rules of Chamberlain[5, 6] with gestation-specific amniotic fluid index standards in detecting abnormalities in amniotic fluid volume.

Methods

A group of 791 patients with normal pregnancies was used to assign limits to the amniotic fluid index and maximum vertical pocket. Patients were considered normal if infant birth weight was between the 10th and 90th percentiles according to California standards,[14] no fetal anomalies were present, and the 5-minute Apgar score was >6. Patients with twins, diabetes, hypertension, bleeding, preterm labor, fetal anomalies, or ruptured membranes were excluded. Only patients with satisfactory obstetric dating were included; a certain and normal last menstrual period plus either a confirmatory pelvic examination before 12 weeks or a confirmatory ultrasonogram between 8 and 24 weeks were acceptable dating methods. The study was cross-sectional: a single examination of each patient was used.

Ultrasonographic examinations were performed with an Ultramark IV (ADR, Bothell, Wash.) with linear transducers (3.5 and 5 Mhz). The maximum-vertical-pocket depth was obtained by measuring the depth of the single deepest unobstructed amniotic fluid pocket visible with the transducer kept parallel to the patient's sagittal plane. The amniotic fluid index was calculated as the sum of the maximum-vertical-pockets obtained in each of four quadrants of the uterus, as previously described.[12] This technique is similar to that described by Phelan et al.[9] except that only amniotic fluid pockets completely clear of cord or extremities were measured. When amniotic fluid index values <100 mm were observed the average of three measurements was re-

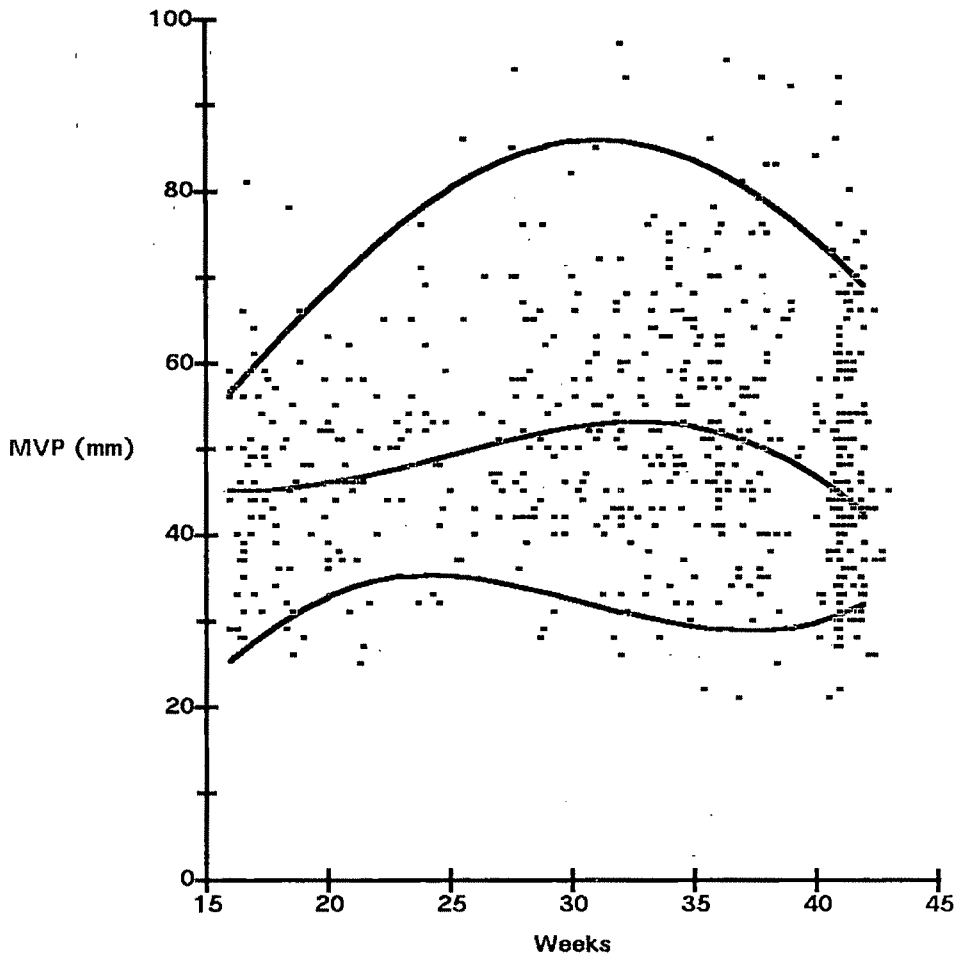


Fig. 2. Maximum-vertical-pocket *(MVP)* data points from normal patients plotted against gestational week. *Upper, middle, and lower* lines represent 95th, 50th, and 5th percentiles, respectively.

Table I. Oligohydramnios: uncorrected maximum-vertical-pocket technique versus amniotic fluid index

Maximum vertical pocket	*Amniotic fluid index*	
	Normal	*Oligohydramnios**
Normal†	1010	44
Oligohydramnios‡	31	32

*Patients whose amniotic fluid index was <5th percentile.
†Patients whose maximum vertical pocket was ≥3 cm.
‡Patients whose maximum vertical pocket was <3 cm.

Table II. Polyhydramnios: uncorrected maximum-vertical-pocket technique versus amniotic fluid index

Maximum vertical pocket	*Amniotic fluid index*	
	Normal	*Polyhydramnios**
Normal†	1026	29
Polyhydramnios‡	15	22

*Patients whose amniotic fluid index was >95th percentile.
†Patients whose maximum vertical pocket was ≤8 cm.
‡Patients whose maximum vertical pocket was >8 cm.

corded to minimize the intraobserver variation encountered with relative oligohydramnios.[12, 15]

The data from the amniotic fluid index observations in the normal patient group were not normally distributed. Logarithmic transforms were used to normalize the variance in each gestational period before analysis. The mean and standard deviation of the log amniotic fluid index was calculated for each week of gestation. A 90% confidence interval (5th to 95th percentiles) was chosen to define "normal." The critical value for oli-

gohydramnios was defined as the 5th percentile. The critical value for polyhydramnios was defined as the 95th percentile. The critical values for abnormal amniotic fluid index were then calculated from the data base stratified by gestational week.

Critical values for the maximum-vertical-pocket were assigned similarly. First, pan-gestation maximum-vertical-pocket values were determined as proposed by Chamberlain et al.[5] by calculating the mean and standard deviation of the maximum-vertical-pocket observations from the entire sample. The 1st (20 mm), 5th (30 mm), 95th (80 mm), and 99th percentiles (93 mm) were computed (uncorrected values). Second, the data set was stratified by pregnancy week and critical values (5th and 95th percentiles) were assigned by gestational age (corrected values).

Fig. 1 illustrates the critical values (5th and 95th percentiles) for the amniotic fluid index from 16 to 42 weeks determined from the normal patient group. Two-way analysis of variance demonstrated a highly statistically significant variation in normal amniotic fluid index values from week to week during gestation ($F = 4.22$, $p < 0.00001$). Fig. 2 depicts the 5th, 50th, and 95th percentiles for the maximum-vertical-pocket in normal patients. Analysis of variance resulted in a weakly significant variation in mean maximum vertical pocket across gestation ($F = 2.2$, $p < 0.05$) but no two gestational segments were statistically distinct (Bonferroni test for multiple comparisons, $p > 0.05$).

The critical values (5th and 95th percentiles) of the amniotic fluid index and maximum-vertical-pocket were then applied to a separate high-risk population of 1178 patients scanned for a variety of indications. Because the amniotic fluid index has been shown to be linearly proportionate to amniotic fluid volume,[11] the amniotic fluid index was used as the volume standard against which the maximum-vertical-pocket criteria were compared. Statistical analysis was performed with a computer-based software package (SPSS), using two-tailed analyses with probability values <0.05 considered significant.

Results

A total of 76 patients (7%) in the test population had oligohydramnios as defined by the amniotic fluid index. The efficiency of the maximum-vertical-pocket technique (uncorrected limit, 30 mm) in correctly detecting oligohydramnios is presented in Table I. Only 32 (42%) of patients with oligohydramnios were correctly identified, whereas 31 patients with normal fluid were incorrectly diagnosed as having decreased amniotic volume. The results among the 51 patients with polyhydramnios were similar (Table II). True-positive diagnoses occurred in 22, whereas 15 normal patients were incorrectly identified as having excessive amniotic fluid.

Table III. Sensitivity and specificity of maximum-vertical-pocket technique in detecting oligohydramnios and polyhydramnios as defined by abnormal amniotic fluid index

Maximum vertical pocket	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*False-positive rate (%)*
<1 cm	5	100	100	95
<3 cm	42	97	51	58
<5th percentile	43	97	52	57
>8 cm	43	99	59	57
>95th percentile	49	98	41	51

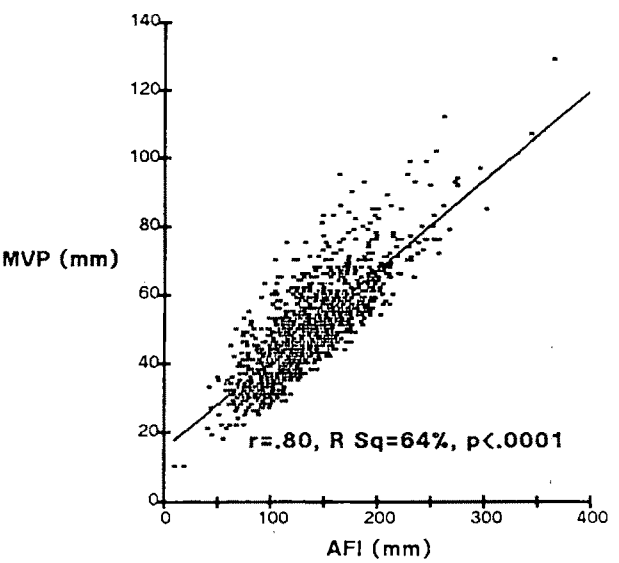


Fig. 3. Amniotic fluid index *(AFI)* and corresponding maximum-vertical-pocket *(MVP)* values compared (high-risk patients).

The sensitivity, specificity, and predictive values of the maximum-vertical-pocket criteria in detecting abnormal amniotic fluid volumes are shown in Table III. Use of a single limit (30 mm) for the maximum-vertical-pocket at all gestations resulted in a sensitivity for detection of oligohydramnios of only 42%. Narrowing the definition of oligohydramnios to the "1 cm rule" lowered sensitivity to 5%. Use of gestation-corrected values for maximum-vertical-pocket (percentiles) did not significantly improve the sensitivity (43% to 49%) and low

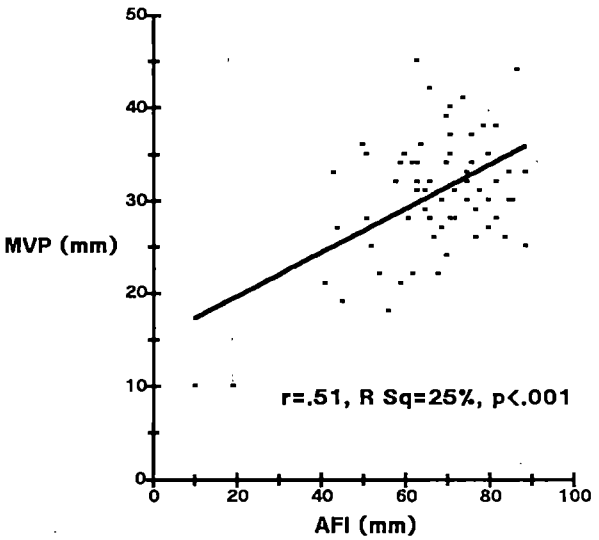


Fig. 4. Amniotic fluid index and maximum-vertical-pocket *(MVP)* values in patients with oligohydramnios (high-risk patients).

positive predictive values. However, the specificity of all maximum-vertical-pocket criteria was uniformly high (97% to 100%).

Fig. 3 shows the relationship of the amniotic fluid index and maximum-vertical-pocket in the test population. The linear correlation is statistically significant, but the regression curve explains only 64% of the variance. Splay from the regression line is marked at the lower (amniotic fluid index < 75 mm) and upper (amniotic fluid index > 250 mm) ends of the range. In patients with oligohydramnios (Fig. 4), the correlation coefficient relating amniotic fluid index and maximum vertical pocket was especially poor ($r = 0.51$).

Comment

Effective use of amniotic fluid volume assessment in monitoring high-risk pregnancy depends on the accuracy of the measures used. Both the single-pocket technique and the four-quadrant methods have been shown to correlate well with neonatal outcome.[1, 5, 6, 9, 10, 16-18] However, this study addressed the issue of accuracy of volume quantitation. The accuracy of single amniotic fluid pocket measurement was compared with the four-quadrant technique, which has been shown to predict volume accurately in the laboratory.[11]

The widely used maximum-vertical-pocket technique has the advantage of ease of use, but this study indicates that currently recommended standards for the maximum-vertical-pocket (2 and 8 cm "rules") are insufficiently sensitive for ultrasonographic screening of amniotic fluid volume. Even when the critical maximum-vertical-pocket values were adjusted for gestational age, the maximum-vertical-pocket sensitivity for oligohydramnios and polyhydramnios was below 50%. Moreover, false-positive diagnoses among patients with normal amniotic fluid approached 50%. These findings confirm those of Bottoms et al.[8] and Rutherford et al.[10]

The inaccuracy of a single-pocket measurement in assessment of amniotic fluid volume is emphasized in patients with oligohydramnios. In this group the correlation between maximum-vertical-pocket and amniotic fluid index was poor. Hoddick et al.[7] reported similarly low sensitivity in detection of intrauterine growth retardation in patients with oligohydramnios whereas Rutherford et al.[10] demonstrated that the amniotic fluid index offers more reliability and sensitivity in this important group of patients.

Ideally, these studies should be performed with controlled volume infusions into the amniotic space of human subjects. Until studies that correlate ultrasonographic measurements of fluid pockets and actual amniotic fluid volume in human pregnancy are available, the amniotic fluid index currently provides the most accurate and reliable method of screening for amniotic fluid volume abnormalities.

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Randomized investigation of magnesium sulfate for prevention of preterm birth

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One hundred fifty-six women with preterm labor between 24 and 34 weeks' gestation were randomized to receive either intravenous magnesium sulfate or no tocolytic therapy. Magnesuim sulfate infusions of up to 3 gm/hr were used in 76 pregnancies and resulted in a mean serum magnesium concentration of 5.5 ± 1.4 mEq/L (mean ± SEM). Compared with 80 control pregnancies, magnesium sulfate tocolysis had no significant effect on duration of gestation, birth weight, neonatal morbidity, and perinatal mortality. We conclude that clinically safe infusions of magnesium sulfate are ineffective when used to prevent preterm birth. (AM J OBSTET GYNECOL 1990;163:767-72.)

Key words: Magnesium sulfate, preterm labor

Effective methods for treatment of preterm labor have become major goals in modern obstetrics because preterm birth is the leading cause of infant morbidity and mortality. A significant cause of preterm birth, labor without ruptured membranes or other obstetric complications necessitating intervention, has been the focus of several pharmacologic approaches aimed at inhibition of uterine contractions. Agents that were used include ethanol,[1-4] prostaglandin synthetase inhibitors,[2, 5, 6] various β-adrenergic sympathomimetics,[7-13] calcium channel blockers,[14] and magnesium sulfate.[11-13, 15-17]

Side effects and clinical conditions that contraindicate the use of β-sympathomimetics have recently directed the focus of attention to the use of magnesium sulfate for the inhibition of preterm labor because high concentrations of magnesium ion inhibit uterine contractility. Specifically, concentrations of 8 to 10 mEq/L were observed to reduce the frequency of in vitro uterine muscle contraction, whereas magnesium levels of 20 mEq/L were necessary for complete cessation of activity.[18] Several studies[11-13, 15-17] have suggested that magnesium sulfate is a reasonably safe and effective agent for tocolysis, although no large randomized investigations comparing this therapy with untreated controls have been reported. We sought to determine if clinically safe magnesium concentrations (i.e., those <8 mEq/L, at which level skeletal muscle paralysis occurs) were effective in preventing preterm birth when compared with untreated controls.

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6/6/22324

Material and methods

Subjects for study were from the population of women who came to the obstetrics service at Parkland Memorial Hospital in Dallas between October 1987 and May 1989. Criteria for enrollment included: (1) preterm labor defined by regular uterine contractions as-

Table I. Clinical characteristics in pregnancies randomized to magnesium sulfate tocolysis compared with controls

Characteristic	*Magnesium sulfate*		*Control (%)*		Comparison
	No.	*%*	*No.*	*%*	
No. of pregnancies	76	100	80	100	—
Twin gestations	2	3	9	11	NS
Total infants	78		89		NS
Maternal age, yr (mean ± SEM)	20.6 ± 0.5		21.3 ± 0.5		NS
Nulliparous women	24	32	28	35	NS
Black	43	57	34	43	NS
White	18	24	26	30	NS
Hispanic	14	18	19	23	NS
Prior preterm birth*	20	26	15	19	NS

*Birth weight <2500 gm.

Table II. Study entry characteristics in pregnancies randomized to magnesium sulfate tocolysis compared with controls

Entry characteristics	*Magnesium sulfate*		*Control*		Comparison
	No.	*%*	*No.*	*%*	
Gestational age at entry, wk (mean ± SEM)	29.9 ± 0.3		30.1 ± 0.3		NS
Cervical dilatation					
Mean ± SEM (cm)	2.2 ± 0.1		2.3 ± 0.1		NS
1 cm	16	21	13	16	NS
2 cm	29	38	35	44	NS
3 cm	20	26	23	29	NS
4 cm	7	9	5	6	NS
Cervical effacement					
Mean ± SEM (%)	45 ± 2.6		52 ± 2.7		NS
<25%	23	30	18	23	NS
26%-50%	38	50	37	46	NS
51%-75%	9	12	13	16	NS
76%-100%	6	8	12	15	NS

sociated with cervical dilatation of at least 1 cm but <5 cm, (2) gestational age between 24 and 34 weeks; (3) intact fetal membranes, and (4) no maternal or fetal complications necessitating delivery. Women who fulfilled these criteria were asked to participate and those who gave informed written consent were enrolled in the investigation, which was performed under the auspices of the Institutional Review Board on Human Research for the University of Texas Southwestern Medical Center at Dallas and Parkland Memorial Hospital. The use of magnesium sulfate for tocolysis at our hospital was restricted to this investigation.

Patients were assigned to treatment or control groups by means of a random number table with group allocation predetermined and placed in consecutively numbered and sealed envelopes. Those randomized to the treatment group received 4 gm of magnesium sulfate in a 20% solution as an intravenous loading dose followed by an infusion of 2 gm/hr. The infusion rate was increased to 3 gm/hr if uterine contractions persisted 1 hour after commencement of therapy. Intravenous magnesium sulfate was continued for 24 hours and no other drug therapy was used during or subsequent to these infusions. Women with recurrent preterm labor at a later date were eligible for a second treatment with intravenous magnesium sulfate. Women assigned to the control group received intravenous physiologic saline solution at a rate of 80 ml/hr for 24 hours.

All women enrolled in the study had continuous electronic fetal heart rate monitoring for 12 to 24 hours and were observed in the labor suite for a minimum of 24 hours. All women who were undelivered in both groups were hospitalized until 34 weeks' gestation in the antepartum pregnancy unit. Laboratory tests for all women included real-time ultrasonographic examination, urinalysis, hematocrit, serum creatinine, glucose, and electrolyte studies. Magnesium level determinations were repeated serially in women randomized to this treatment group.

Therapy was considered unsuccessful if the fetal

Table III. Selected outcomes in pregnancies randomized to magnesium sulfate tocolysis compared with controls

Selected outcomes	*Magnesium sulfate*		*Control*		*Comparison*
	No.	*%*	*No.*	*%*	
Gestational age at delivery mean ± SEM (wk)	33.8 ± 0.5		33.0 ± 0.5		NS
24-26 wk	2	3	4	5	NS
27-29 wk	10	13	11	14	NS
30-32 wk	19	25	14	18	NS
33-35 wk	15	20	30	38	0.02
≥36 wk	30	39	21	26	NS
Time gained in utero Mean ± SEM (days)	26.6 ± 3.0		22.4 ± 2.5		NS
≤1 day	22	29	22	28	NS
2-7 days	14	18	7	9	NS
8-28 days	14	18	23	29	NS
≥28 days	26	34	28	35	NS

membranes ruptured, cervical dilatation progressed to >4 cm, contractions persisted longer than 30 minutes at the maximum magnesium dose with continued cervical dilatation, or maternal side effects necessitated discontinuation of the drug. Maternal side effects such as muscle weakness and symptomatic hypotension prompted a reduction in magnesium dose. If a progressive reduction in dosage was ineffective in relief of these symptoms, or if maternal respiratory depression was noted, use of magnesium sulfate was discontinued.

Entry characteristics and outcome variables were analyzed with Student's t test, χ^2 analysis, or Fisher's exact test of probability. Results in which the probability of a type 1 error were <0.05 were considered significant.

Results

A total of 156 pregnancies were included during the 19-month study; 76 were randomized to receive magnesium sulfate and 80 to the control group. The clinical characteristics of the two study groups are shown in Table I. There were no significant differences between the two groups with respect to maternal age, parity, or racial composition. Similarly, there was no significant difference in the incidence of prior preterm birth defined as birth weight <2500 gm. Table II shows gestational age, cervical dilatation, and effacement at entry into the study for pregnancies randomized to receive magnesium sulfate compared with controls. There were no significant differences in any of these study entry characteristics.

Table III summarizes selected pregnancy outcomes including gestational age at delivery and days gained in utero. Significantly fewer pregnancies randomized to magnesium sulfate were delivered between 33 and 35 weeks' gestation ($p = 0.02$) compared with the control group. However, all other comparisons were not significant, including rates of cesarean section, which were 16.4% and 17.8%, respectively, for magnesium sulfate and control groups.

Selected neonatal outcomes according to maternal treatment group are summarized in Table IV. Results in pregnancies randomized to receive magnesium sulfate did not differ significantly from the control group with respect to birth weight, 5-minute Apgar scores, or number of days of neonatal intensive care. Similarly, indices of serious neonatal morbidity, such as respiratory distress, intracranial hemorrhage, and necrotizing enterocolitis, were not affected by preterm labor management. Two intrapartum fetal deaths occurred in pregnancies randomized to magnesium sulfate; one resulted from abruptio placentae several weeks after tocolytic therapy, and multiple anomalies were present in the other stillbirth. As shown in Table V, there were a total of six neonatal deaths; 5 occurred in the magnesium sulfate group. Factors implicated in these deaths included complications of immaturity ($n = 4$) and congenital malformations ($n = 2$). One death occurred in each treatment group after 28 days of life but before discharge.

Of the 76 women randomized to receive magnesium sulfate, 62% received the maximum dose of 3 gm/hr. The mean serum magnesium concentration in the treatment group was 5.5 ± 1.4 (SEM) mEq/L. This value reflects the mean of at least three measurements per pregnancy at the maximum magnesium sulfate infusion rates. Magnesium infusions were discontinued in eight women (11%) because of toxicity that included generalized muscle weakness ($n = 6$), respiratory depression ($n = 1$), and systemic hypotension ($n = 1$).

Comment

Side effects, in addition to the clinical conditions that contraindicate the use of β-sympathomimetics, have

Table IV. Selected neonatal outcomes in pregnancies randomized to magnesium sulfate tocolysis compared with controls

Neonatal outcomes	*Magnesium sulfate*		*Control*		*Comparison*
	No.	*%*	*No.*	*%*	
Birth weight (gm)					
Mean ± SEM (gm)	2264 ± 93		2204 ± 77		NS
750-1000 gm	3	4	4	5	NS
1001-1250 gm	4	5	2	3	NS
1251-1500 gm	6	8	6	8	NS
1501-1750 gm	12	16	6	8	NS
1751-2000 gm	8	11	9	11	NS
2001-2250 gm	5	7	14	10	NS
2251-2500 gm	8	11	10	13	NS
≥2501 gm	31	41	28	35	NS
5 min Apgar score (mean ± SEM)	8 ± 0.2		8 ± 0.2		NS
Neonatal hospital Mean ± SEM (days)	13.8 ± 1.9		19.7 ± 3.1		NS
Intensive care	5	7	12	15	NS
Respiratory distress					
None	3	4	10	13	NS
Required ventilator	15	20	15	19	NS
Intracranial hemorrhage	4	5	4	5	NS
Necrotizing enterocolitis	4	5	3	4	NS
Stillbirth	2	3	0		NS
Neonatal death	5	7	1	1	NS
Infant death*	1	1	1	1	NS

*After 28 days of life but before discharge.

Table V. Descriptions of neonatal deaths

Case	*Gestational age (wk)*			*Comment*
	Study group	*At entry*	*At delivery*	*Days gained*
1	Magnesiun sulfate	27	27	0	1150 gm, Apgar scores 1/1/9, RDS, died day 4
2	Magnesiun sulfate	25	25	2	740 gm, Apgar scores 4/5, immaturity, died day 3
3	Magnesiun sulfate	28	28	4	895 gm, Apgar scores 1/4/7, IVH, immaturity, died day 3
4	Magnesiun sulfate	32	33	6	1515 gm, Apgar scores 7/4/4, diaphragmatic hernia, died day 6
5	Magnesiun sulfate	32	32	5	1625 gm, Apgar scores 4/6, multiple congenital anomalies, died day 10
6	Control	24	25	11	800 gm, Apgar scores 2/1/1, immaturity, died day 1

RDS, Respiratory distress syndrome; *IVH,* intraventricular hemorrhage.

served to focus attention on the use of magnesium sulfate given intravenously as an alternative tocolytic drug. In 1959 Hall et al.[18] demonstrated that strips of human gravid uterine muscle had reduced contractility in the presence of magnesium ion. Specifically, concentrations of magnesium approximating 8 to 10 mEq/L were observed to reduce the frequency of in vitro uterine muscle contractions. Complete inhibition of uterine activity, however, required magnesium concentrations of approximately 20 mEq/L. Other investigators have shown in humans that concentrations of 8 to 10 mEq/L result in loss of patellar reflexes with respiratory depression occurring at 10 mEq/L and respiratory arrest at 12 mEq/L or higher concentrations.[19]

The first centers in the United States to use magnesium for tocolysis were the Columbia-Presbyterian Medical Center, where the drug has been used routinely since 1969, and the University of Virginia, where it has been used since 1970.[16] In 1977 Steer and Petrie[15] evaluated intravenous magnesium sulfate given for to-

colytic therapy to 31 women for preterm labor and found such therapy effective in stopping uterine contractions for at least 24 hours. The magnesium sulfate dosage was 4 gm of a 10% solution followed by 2 gm/hr. Spisso et al.[17] subsequently also reported use of magnesium sulfate to be effective in delaying delivery 48 hours or longer in a nonrandomized study that included 119 pregnancies with preterm labor and intact fetal membranes.

In a retrospective study Elliott[20] reported successful use of magnesium sulfate for inhibition of preterm labor in 274 pregnancies. Magnesium sulfate was infused in dosages of up to 3 mg/hr with serum magnesium concentrations that ranged as high as 10 mEq/L. The frequency of such toxic levels and the consequences were not specifically cited, although Elliott concluded that the side effects of magnesium infusions compared favorably with those reported for β-sympathomimetics. He also observed empirically that magnesium serum levels of approximately 4 to 6 mEq/L were usually sufficient to inhibit uterine contractions. More recently Hollander et al.[13] evaluated the use of magnesium sulfate as a tocolytic agent with even higher dosages. In their study the efficacy of magnesium sulfate was analyzed in relation to ritodrine hydrochloride. The mean magnesium sulfate dosage required to achieve tocolysis was reported to be 4.5 gm/hr and the mean magnesium level resulting in tocolysis was 6.6 mg/dl (5.3 mEq/L). The dosage regimen used in this investigation included a 4 gm bolus injection of magnesium sulfate followed by 2 gm/hr intravenously. The infusion rate was increased at 30-minute intervals by 1 gm/hr and to a maximum infusion of 5 gm/hr. After successful tocolysis the infusion rate was decreased to the lowest effective rate required to maintain uterine quiescence and also maintain serum magnesium levels in the range of 6 to 8 mg/dl. Such infusions were then continued for a period of 12 hours. Among 33 women who were treated only with magnesium sulfate, the reported regimen necessitated a decrease in dosage because of lethargy in 15 women (45%). The experience of these investigators suggests that effective uterine contraction–inhibiting concentrations of magnesium must be near toxic levels to anticipate a clinical uterine effect. The margin between safety and efficacy of magnesium sulfate infusions for tocolysis appears to be quite narrow.

To date, there has been only one published randomized investigation in which magnesium sulfate tocolysis was compared with untreated controls.[11] Cotton et al. randomized a total of 54 women with preterm labor between 26 and 34 weeks' gestation to treatment with magnesum sulfate, placebo, or terbutaline. They defined successful tocolysis as postponement of delivery for at least 48 hours. Patients assigned to the magnesium sulfate group (n = 16) received 4 gm intravenously over 15 minutes and then a continuous infusion of 2 gm/hr. They found no significant differences among the three treatment groups with regard to delay of delivery 48 hours or longer.

Our study was prompted because magnesium sulfate is frequently used as a tocolytic agent but has not been studied extensively with randomization and untreated control subjects. During the study period 23,658 women were delivered at our hospital. On the basis of a previous survey of low birth weight at our hospital, we estimate that a maximum of 294 (1.3%) pregnancies were eligible for randomization during this investigation. However, patients commonly declined randomization and clinical developments before written consent could be obtained frequently excluded potential patients. It is important to note that women who met the study inclusion criteria were consistently offered participation in this investigation. Indeed, 156 randomized pregnancies may seem like a small number; however, this population represents the largest single center randomized study to compare a tocolytic drug with no treatment.

We elected to use modest infusion rates of magnesium sulfate to avoid the unacceptably high incidence of toxicity reported with infusion rates in excess of 3 gm/hr. The majority (62%) of the women received infusions of 3 gm/hr and achieved serum magnesium concentrations well within the range of values previously reported to be effective for inhibition of preterm uterine contractions. Specifically, the maximum magnesium concentration in this study was 5.5 ± 1.4 mEq/L (mean ± SEM); this level compares favorably with the results of Elliott[20] (4 to 6 mEq/L) and Hollander et al.[13] (6.6 mg/dl, equivalent to 5.3 mEq/L). We believe that magnesium ion in sufficient concentrations can inhibit muscle activity, including the uterus, but found that concentrations less than these levels do not effectively delay delivery in women with pregnancies complicated by preterm labor. Moreover, we were unable to document any perinatal benefit when magnesium sulfate infusions were used to prevent preterm birth compared with untreated control subjects. We therefore conclude that magnesium sulfate infusions resulting in maximum serum concentrations of magnesium equal to 5.5 mEq/L are ineffective in the prevention of preterm birth.

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Fetal gastroschisis and omphalocele: Is cesarean section the best mode of delivery?

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There has always been controversy regarding the mode of delivery of fetuses with abdominal wall defects. Prior studies may have been biased in this evaluation as a result of the effects of delay in repair, transport of the fetus to level III facilities, and antenatal diagnosis compared with an unsuspected diagnosis. The purpose of this study was to evaluate mode of delivery at level III institutions with access to complete care to determine if cesarean section improved outcome. One hundred eight infants were treated in the study period for abdominal wall defects. Fifty-six infants met all criteria for admission to the study. No difference in neonatal morbidity or mortality was identified. No difference was found in infants who were born by elective cesarean section compared with infants delivered after labor ensued. In conclusion, we found no evidence that cesarean section or avoidance of labor improved outcome in fetuses with uncomplicated abdominal wall defects. (AM J OBSTET GYNECOL 1990;163:773-5.)

Key words: Gastroschisis, omphalocele, mode of delivery

The accuracy of prenatal diagnosis of many congenital abnormalities has been dramatically improved with advances in high-resolution ultrasonography. With an increasing frequency of antenatal diagnosis of certain fetal abnormalities, planning appropriate management has become an area of much research. Frequently there is no clear consensus for management of specific fetal malformations.

This problem exists with respect to the most appropriate mode of delivery of infants with gastroschisis or omphalocele. Several authors have found no difference between vaginal and abdominal delivery.[1-5] Others have reported that cesarean delivery decreases both neonatal morbidity and mortality.[3, 7] All previous studies, however, suffer from the presence of multiple confounding variables.[8]

The purpose of this study was to evaluate route of delivery on outcome in infants with gastroschisis or omphalocele while eliminating significant confounding variables.

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Table I. Indications for exclusion ($N = 52$)

Indications	*No.*
Transported from other facility	36
Multiple anomalies	
Cardiac	6
Other	1
Chromosomal abnormalities	
Trisomy 18	3
Trisomy 13	2
Extracorporeal liver	4

Material and methods

The charts of all infants treated for either omphalocele or gastroschisis, as defined by Moore and Stokes[9], between January 1984 through October 1989 were reviewed. Three level III institutions were the source of the patient population: the University of California at Irvine Medical Center, Long Beach Memorial Womens Hospital, and Huntington Memorial Hospital of Pasadena. Patients were excluded if they were transported after delivery from other institutions, or had multiple congenital anomalies, chromosomal abnormalities, or an extracorporeal liver.

The following factors were statistically analyzed: antenatal diagnosis, estimated gestational age at delivery, route of delivery, mean birth weight, delay in repair of the defect after birth, neonatal length of stay, 5-minute Apgar scores, and neonatal mortality.

Table II. Comparison by delivery mode

Factor	*Vaginal delivery (N = 23)*	*Cesarean section (N = 33)*
Antenatal diagnosis	10	23*
Omphaloceles	4	4
Gestational age (wk)	36.3 ± 3.2	36.0 ± 3.1
Birth weight (gm)	2554 ± 897	2608 ± 623
Delay in surgery (hr)	6.34 ± 4.5	5.24 ± 4.7
Neonatal length of stay of survivors (days)	28.24 ± 24.7	35.2 ± 27.1
5 Min Apgar score	8.6 ± 0.6	8.6 ± 0.8
Mortality	1	3

Values are represented as mean ± SD.
*$p < 0.02$

Table III. Neonatal complications

Complication	*Vaginal delivery (N = 14)*	*Cesarean section (N = 20)*
Necrotizing enterocolitis	3	4
Meconium aspiration	0	3
Sepsis	2	3
Respiratory distress syndrome	2	3
Staged closure	7	7

Table IV. Comparison of patients with elective cesarean sections with patients who entered labor

Factor	*Elective cesarean section (N = 23)*	*Labor (N = 33)*
Antenatal diagnosis	23	15
Omphalocele	3	5
Birth weight (gm)	2648 (575)	2543 (842)
Gestational age (wk)	36.1 (1.4)	36.2 (3.2)
Neonatal length of stay of survivors (days)	35.2 (31.2)	30.1 (24.6)
Mortality	3	1

Data are represented as mean ± SD.

Two groups were established to determine if labor adversely affects infants with abdominal wall defects: those infants delivered after labor had begun (i.e., the vaginal group and those delivered by cesarean section after labor ensued) and those delivered by elective cesarean section. The same parameters were statistically analyzed between those patients delivered by cesarean section with or without labor.

Statistical analysis was performed with the Student *t* test.

Results

One hundred eight infants were treated for gastroschisis or omphalocele during the study interval. Fifty-two patients were excluded from the study because they did not meet criteria (Table I). Fifty-six met all criteria for study evaluation. There were no differences in gestational age at delivery, birth weight, Apgar score at 5 minutes, neonatal length of stay, or delay in surgical repair of the defect between patients delivered vaginally and those delivered by cesarean section (Table II). However, antenatal diagnosis was found to be more frequent in patients delivered by cesarean section ($p < 0.02$). All patients delivered by elective cesarean section had the noted defect as one of the indications for cesarean delivery. In addition, five of the infants were breech, three mothers had previous cesarean sections, and one had pregnancy-induced hypertension. No difference in neonatal morbidity or mortality was identified between the groups. There were no significant differences in neonatal complications between the groups (Table III). Further analysis of patients delivered with or without labor failed to reveal any differences (Table IV). Labor did not influence outcome. There were no differences in outcome between institutions, and neonatal outcome was the same with either gastroschisis or omphalocele as the fetal abnormality. Infants who were delivered closer to term (>34 weeks) were also separately evaluated and no differences were found.

Comment

As the ability to diagnose congenital abnormalities has improved, questions of management, intervention, and ethics are being encountered. Frequently, these questions are difficult to resolve when counseling a family with a specific fetal abnormality. The optimal route of delivery for patients with fetal abdominal wall defects is one such difficult area. Previous studies on mode of delivery of these infants have been potentially biased in several ways. These biases include delivery of the infant at a level I or II facility with subsequent transport to a level III institution, delay in surgical repair, and appropriate neonatal resuscitation capability. Consequently, interpretation of outcome data may be misleading. In this study we analyzed infants with gastroschisis or omphalocele delivered in an optimal environment for resuscitation and repair and compared vaginal delivery with cesarean section to de-

termine whether delivery mode affected neonatal outcome.

All study participants were delivered in a level III institution with readily available perinatologist, neonatologist, and pediatric surgeon. Infants with lethal congenital malformations, chromosomal abnormalities, or extracorporeal livers were excluded. Although studies do not exist with regard to infants with extracorporeal livers, we thought that this factor could significantly alter the data. There were only four cases in our study with extracorporeal livers that did not also have a chromosomal abnormality or other multiple anomalies. Inclusion of these four cases did not result in significant differences in outcome.

A randomized prospective study would be the best method to determine whether mode of delivery affects outcome in infants with abdominal wall defects. However, the above confounding variables should be assessed if such a study is performed.[7,8]

When the mode of delivery of a fetus with a structural abnormality is evaluated, the possibility exists that labor itself may have an adverse affect on outcome. Therefore we evaluated the cesarean section group by comparison of those with labor and those without labor; no difference in fetal outcome was observed. Even when all cases with labor (vaginal delivery and cesarean section) were compared with elective cesarean section without labor, no differences occurred.

In this study no benefit could be established for elective abdominal delivery. There was no difference in morbidity, mortality, length of stay of surviving infants, or overall outcome between the vaginal delivery group and the cesarean section group. Therefore cesarean section in the management of fetal abdominal wall defects should be reserved for obstetric indications only. To achieve the best possible outcome these infants should be delivered in a level III institution with good communication between the perinatal and neonatal teams.

We thank Bharat Shah, MD, for providing information from Huntington Memorial Hospital of Pasadena.

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Acute fetal hemodynamic alterations after intrauterine transfusion for treatment of severe red blood cell alloimmunization

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One of the compensatory hemodynamic mechanisms seen in the anemic human fetus is an increased cardiac output. With Doppler techniques, cardiac output was measured in 21 fetuses before and immediately after 38 intrauterine transfusions for severe red cell alloimmunization. Umbilical venous pressures were measured before and after transfusion; amniotic fluid pressure was also quantitated. After subtraction of amniotic pressure, umbilical venous pressure increased by 1.7 ± 2.8 mm Hg ($p < 0.01$). Left and right ventricular output declined by 19% and 22%, respectively ($p < 0.001$). Four factors are known to affect cardiac output: heart rate, cardiac contractility, preload, and afterload. Fetal heart rate and mean acceleration, a measure of myocardial contractility, were unchanged after transfusion. A calculated mean increase in the fetoplacental volume of 18% in conjunction with an increase in umbilical venous pressure would indicate that cardiac preload was increased. We propose that intravascular intrauterine transfusion leads to an increased cardiac afterload, possibly by increasing blood viscosity. The fetal heart responds to the increased afterload by a decrease in stroke volume, leading to a fall in cardiac output. (Am J Obstet Gynecol 1990;163:776-84.)

Key words: Red cell alloimmunization, intrauterine transfusion, umbilical venous pressure, fetal cardiac output

Red cell alloimmunization results in the progressive destruction of fetal red cells, eventually leading to fetal anemia and hydrops. Compensatory mechanisms by which the fetus responds to this anemia include an increase in cardiac output and alterations in regional blood flow.[1, 2] Although these mechanisms have been studied in the animal fetus with the acute induction and correction of anemia, human studies have been limited to date.

Doppler techniques have been used to study blood flows in the human fetus in a noninvasive fashion. Blood velocities in the descending aorta of anemic fetuses have been found to be higher than those in controls.[3] Other investigators have reported increased umbilical venous flow in the fetus with anemia.[4] These findings are suggestive that the human fetus, like animal models, may respond to anemia with an elevation in cardiac output. With Doppler ultrasonography, Copel et al.[5] reported that cardiac output in anemic fetuses is higher than in control fetuses matched for gestational age. However, these authors could not demonstrate any change in cardiac output 24 hours after correction of anemia by direct intravascular transfusion.[6]

In two reports,[7, 8] an increase in human fetal umbilical venous pressure was detected after intravascular transfusion for red cell alloimmunization. An increase in the fetal blood volume as a result of the intravascular transfusion could not be correlated with the increased umbilical venous pressure. However, Nicolini et al.[7] were able to find that an increase in fetal hematocrit correlated with a rise in umbilical venous pressure.

We postulated that acute alterations in fetal cardiac output may occur in the human fetus soon after correction of anemia. There are four determinants of cardiac output: heart rate, cardiac contractility, preload, and afterload.[9] To better understand the cardiovascular responses to transfusion in the human fetus, we measured cardiac output and assessed its determinants before and after intravascular transfusions for red cell alloimmunization.

Material and methods

The study protocol was approved by the human investigational review boards of Baylor College of Medicine, St. Luke's Episcopal Hospital, and the Harris County Hospital District.

The study population comprised 21 fetuses under-

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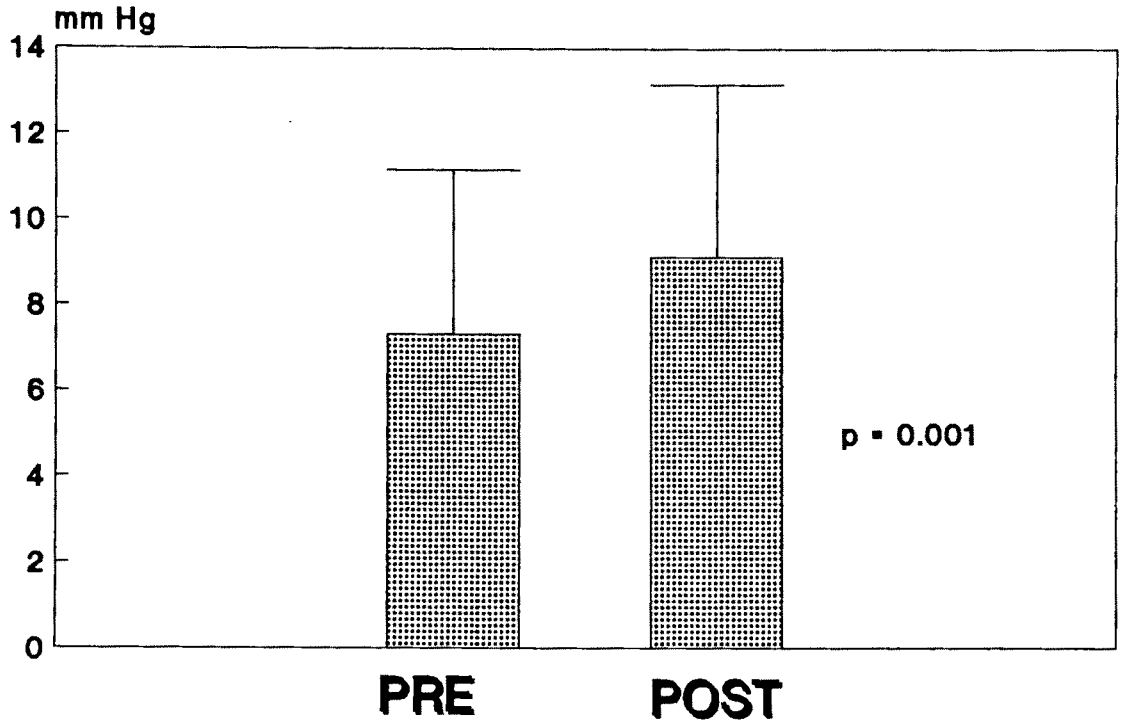


Fig. 1. Corrected umbilical venous pressure before and after transfusion (mean ± SD).

going 38 intravascular transfusions. One pregnancy involved Kell alloimmunization, one involved little "c" disease, and the remaining 19 pregnancies were complicated by anti-D alloimmunization. The number of procedures during which hemodynamic studies were undertaken was as follows: 1 transfusion, 11 fetuses; 2 transfusions, 7 fetuses; 3 transfusions, 1 fetus; 4 transfusions, 1 fetus; and 6 transfusions, 1 fetus. The mean (±SD) gestational age at the time of transfusion was 28.3 ± 4.2 weeks (range, 20.9 to 37.1 weeks). Fetal hydrops was noted at the time of transfusion on 11 occasions. Gestational age in this group of fetuses ranged from 21.0 to 37.1 weeks (mean ± SD, 27.6 ± 4.3 weeks).

Before the intrauterine transfusion, two-dimensional directed pulsed Doppler ultrasound (GE PASS II, General Electric Medical Systems, Milwaukee, Wis.) was used to obtain the time velocity integral of the aorta and main pulmonary artery at the level of the semilunar valve leaflets. A five-chamber view was used to measure the aortic time velocity integral. If the fetus was positioned with its spine posterior, the pulmonary artery was studied in a short-axis view of the great vessels, whereas if the fetal spine was anterior, a sagittal view of the ductal arch was obtained. Real-time imaging was used to adjust the Doppler angle of insonation so as to obtain measurements parallel to the axis of flow. Doppler studies were repeated within 2 hours after completion of the intravascular phase of intrauterine transfusion. All Doppler waveforms were recorded on videotape. Offline analysis was undertaken with a digitalized computer system (Digisonics, Inc., Houston, Tex.). Doppler parameters were determined from at least three consecutive waveforms and results were averaged.

Cardiac stroke volume can be calculated by multiplying the cross-sectional area of the outflow tract of a ventricle by the Doppler time velocity integral.[10] The product of the stroke volume and heart rate is the ventricular output in milliliters per minute. Cardiac output before and after intrauterine transfusion would therefore be calculated by the following equations:

$$\text{Cardiac output pretransfusion} = \text{Valve area}_1 \times \text{TVI}_1 \times \text{HR}_1$$

$$\text{Cardiac output posttransfusion} = \text{Valve area}_2 \times \text{TVI}_2 \times \text{HR}_2$$

where TVI is time velocity integral and HR is heart rate. The greatest limitation in the measurement of fetal ventricular output is related to quantitation of the diameter of valve orifices. The small size of these fetal vessels in conjunction with limitations in lateral ultrasonographic resolution can produce a large degree of error. Inasmuch as the radius of the valve orifice is squared to calculate the cross-sectional area, even the smallest error in measurement will considerably affect the outflow calculation. If we assume that the valve area remains constant, the following equations allow for detection of percent change in ventricular output:

$$\text{Because Valve area}_1 = \text{Valve area}_2$$

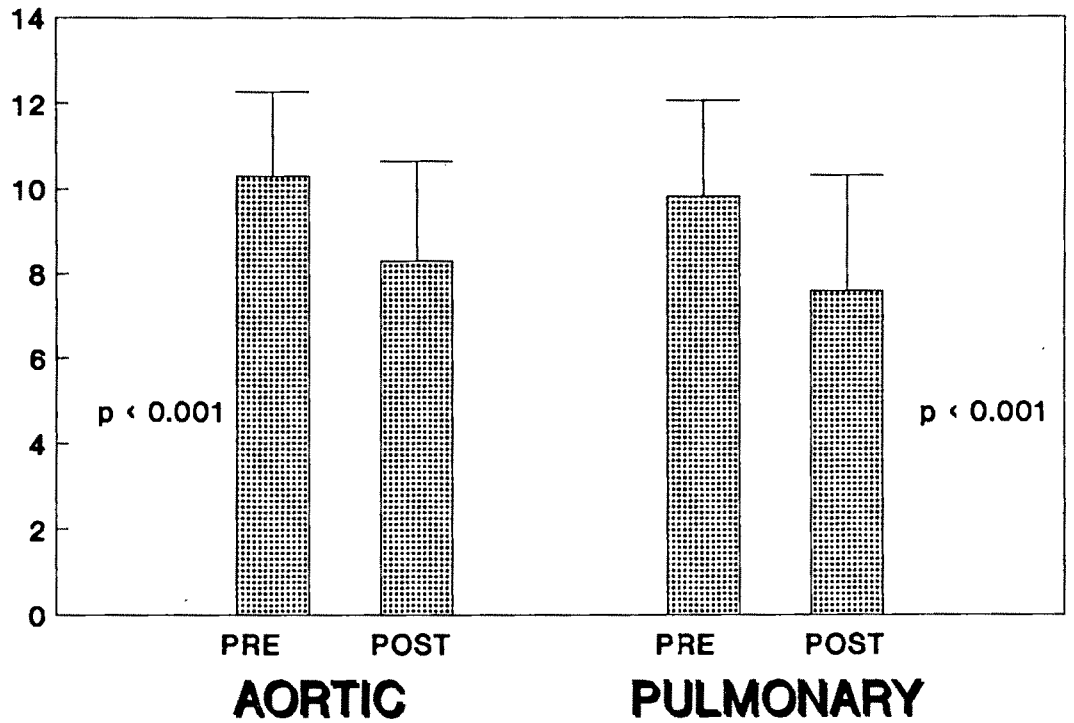


Fig. 2. Time velocity integral before and after transfusion (mean ± SD).

% Change in ventricular output =

$$\frac{(TVI_2 \times HR_2) - (TVI_1 \times HR_1)}{TVI_1 \times HR_1}$$

where TVI is time velocity integral and HR is heart rate. Colocousis et al.[11] have verified this technique in a dog model by showing that changes in left ventricular stroke volume are proportional to alterations of the aortic Doppler time velocity integral.

Noninvasive measurement of myocardial contractility has been limited to such crude parameters as M-mode measurements of changes in chamber size. With the advent of Doppler ultrasonography, waveform analysis of blood flow in the ascending aorta has been found to correlate with standard invasive techniques of left ventricular function.[12] Of the various parameters analyzed, mean acceleration (peak velocity divided by the time interval until peak velocity is achieved) was noted to be an effective measure of myocardial function.[12] Therefore we measured the mean acceleration of the Doppler waveforms from the aorta and pulmonary artery in an attempt to detect any changes in myocardial contractility after intravascular transfusion.

Intravascular transfusion was undertaken in the following manner. The cord insertion was localized with a 3 mHz sector transducer (Acuson 128, Mountain View, Calif.). Under continuous ultrasonographic guidance, a 20-gauge procedure needle was directed into the amniotic cavity. Sterile arterial pressure tubing that had been flushed with saline solution was then connected to the needle. A small amount of flush was introduced to clear the needle of amniotic fluid. Mean amniotic fluid pressure was measured continuously with a Physiocontrol VSM 1 neonatal blood pressure monitor until stable readings were obtained. The procedure needle was directed into the umbilical cord insertion and an initial sample of blood was removed for fetal hematocrit determination. Intravenous pancuronium bromide was administered to effect fetal neuromuscular blockade. A pretransfusion mean umbilical venous pressure was recorded until stable. An intravascular transfusion was undertaken with packed red blood cells until a final fetal hematocrit of 35% to 40% was attained. A final sample of fetal blood was removed, after which a posttransfusion umbilical venous pressure was obtained. As part of a combined transfusion technique,[13] a standard intraperitoneal transfusion was performed. If no amniotic fluid pressure could be obtained during the intravascular portion of the procedure as a result of an anterior placental cord insertion, amniotic fluid pressure was measured at the time of the intraperitoneal transfusion.

Mean amniotic fluid pressure was subtracted from

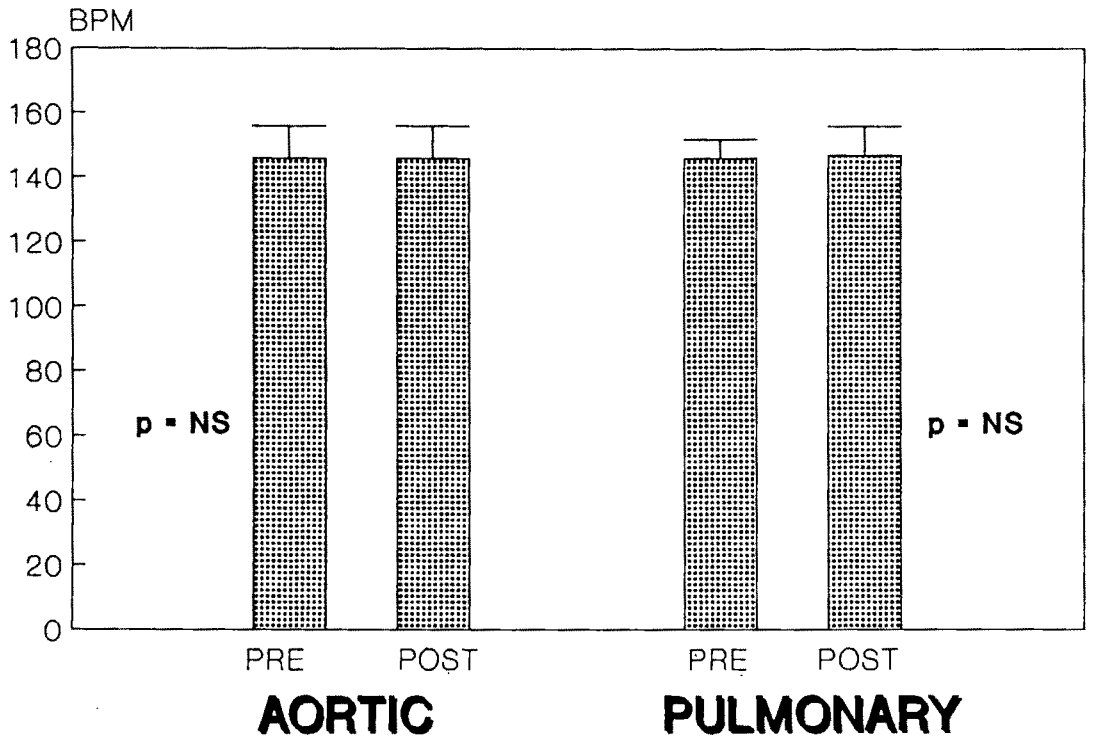


Fig. 3. Heart rate before and after transfusion (mean ± SD).

the corresponding umbilical venous pressure obtained before and after transfusion to derive the corrected umbilical venous pressure. Net volume transfused was calculated by subtracting all sample volumes removed from the volume of transfused blood. Fetoplacental volume was derived from the estimated fetal weight on the basis of ultrasonographic parameters and previously published formulas.[14, 15]

All values are reported as the mean ± SD of the mean. A normal distribution of the data was confirmed by quantile-quantile plots. Paired and unpaired two-tailed Student *t* tests were used for comparisons of data. A p value of <0.05 was considered statistically significant.

Results

The mean initial hematocrit in those fetuses without hydrops at the time of intrauterine transfusion was 27.2% ± 4.9%, whereas the final hematocrit was 36.7% ± 2.8% after a net infusion of 18.4 ± 13.9 ml of packed red cells. This volume represented an increase in the fetoplacental volume of 15.8% ± 10.9%. In those fetuses with hydrops, 35.7 ± 32.4 ml of blood were transfused (fetoplacental volume increase of 21.8% ± 12.4%) to increase the hematocrit from 19.4% ± 4.2% to 33.5% ± 5.3%.

The mean time interval between pretransfusion echocardiograms and intrauterine transfusion was 169 minutes, whereas posttransfusion echocardiograms were undertaken 79 ± 41 minutes after the intravascular phase of the procedure. Only slight fetal movement was noted during the second cardiac study. None of the fetuses exhibited episodes of bradycardia after intrauterine transfusion.

At the time of 32 of the transfusions, the amniotic fluid pressure and pretransfusion and posttransfusion umbilical venous pressures could be measured. A net increase in umbilical venous pressure of 1.7 ± 2.8 mm Hg was noted ($p < 0.01$). Fig. 1 depicts this change.

In 24 cases, Doppler analysis of the aortic outflow tract could be obtained before and after intravascular transfusion. The time velocity integral of the pulmonary valve was noted to decline significantly, whereas heart rate remained unchanged (Figs. 2 and 3). As shown in Fig. 4, a 19% mean decrease in left ventricular output (time velocity integral × heart rate) was noted. Mean acceleration in the aorta was unchanged after transfusion (Fig. 5).

In 23 cases, Doppler analysis of the pulmonary outflow tract could be obtained before and after intravascular transfusion. Pulmonary time velocity integral declined significantly after transfusion, whereas heart rate again showed no change (Figs. 2 and 3). As depicted

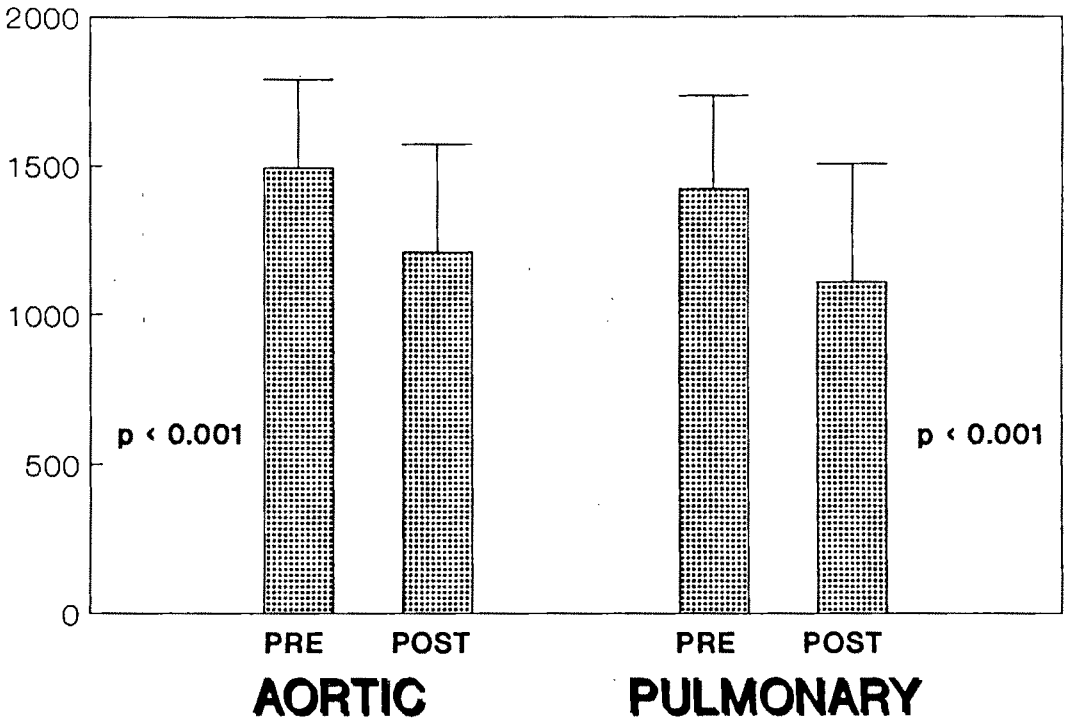


Fig. 4. Left and right ventricular output (time velocity integral × heart rate) before and after transfusion (mean ± SD).

in Fig. 4, the mean fall in right ventricular output (time velocity integral × heart rate) was 22.0%. Pulmonary mean acceleration was not significantly altered after transfusion (Fig. 5).

Because hemodynamic parameters were studied at the time of subsequent procedures in 10 of the 21 fetuses in our series, the possibility that a bias could have been introduced was entertained. For this reason, the effect of intravascular transfusion on left and right ventricular outputs was analyzed separately for the first and subsequent transfusions. At the time of eight initial transfusions, the mean decline in left ventricular output was 32.0% ($p < 0.0001$), whereas seven initial transfusions were associated with a decline in right ventricular output of 34.0% ($p < 0.001$). In 12 subsequent transfusions, left ventricular output declined 10.3% ($p = 0.02$), whereas right ventricular output fell 14.6% ($p = 0.04$). Initial transfusions were associated with a greater fall in left ventricular output than that in subsequent transfusions ($p < 0.001$). This trend was also found for right ventricular output; however, this difference did not reach statistical significance ($p = 0.06$). The differences in ventricular output at first and subsequent transfusions are depicted in Fig. 6.

To examine whether the presence of fetal hydrops affected the overall results of our study, ventricular outputs in nonhydropic fetuses were compared with measurements in hydropic fetuses. No significant difference in decline of left ventricular output was noted (mean decline, 23% versus 20%, respectively; $p = 0.23$). Right ventricular output decreased by 22% in nonhydropic fetuses and by 13% in hydropic fetuses. Again this difference was not found to be statistically significant ($p = 0.76$; Fig. 7).

Comment

In the current study, fetal cardiac output declined after acute correction of anemia by combined intrauterine transfusion. One of the limitations of our study design was that it was both cross-sectional and longitudinal in nature. To determine whether this created a bias in the results we obtained, data obtained from first and subsequent transfusions were analyzed separately. A decline in cardiac output was confirmed in both groups. It would therefore appear that our overall finding that intrauterine transfusion leads to a fall in fetal cardiac output is valid despite the use of repeated measures on some of the fetuses.

Initial transfusions were associated with a greater decline in ventricular output as compared with later transfusions. One possible explanation for this finding is that the nadir of the fetal hematocrit was more likely to be

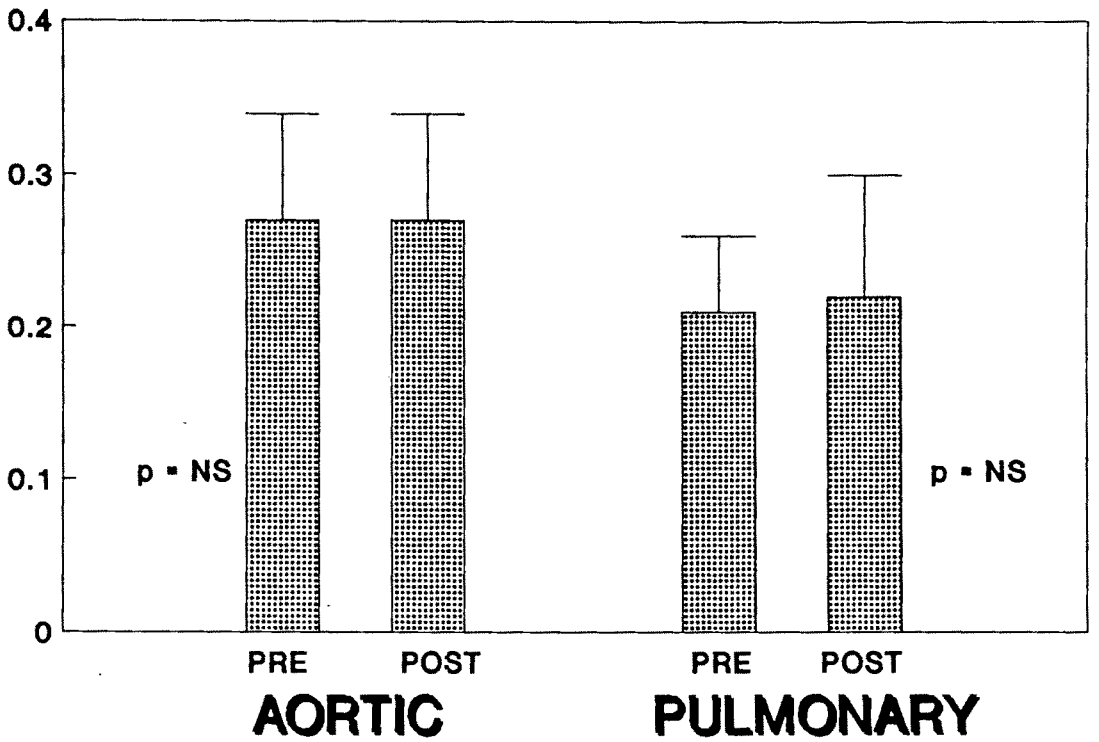


Fig. 5. Aortic and pulmonary mean acceleration before and after transfusion (mean ± SD).

present before the first transfusion before in utero therapy had been initiated. Correction of the hematocrit to a normal value would therefore involve the greatest change in hematocrit and blood viscosity during the first transfusion. Inasmuch as viscosity contributes to cardiac afterload, cardiac output would fall more during first transfusions as compared with subsequent procedures. Animal data would support this explanation. With a radioactive microsphere technique, Fan et al.[1] demonstrated in mongrel dogs that cardiac output decreased as hematocrit was increased. Murray and coworkers[16] also studied the interaction between hematocrit and cardiac output. They induced hypervolemic polycythemia in mongrel dogs with transfusions of red cells. Isovolemic exchanges with 6% dextran in saline solution were then used to lower the hematocrit. The authors confirmed an inverse relationship between cardiac output and hematocrit.

To postulate an explanation for the decline in cardiac output found in the current study, one must examine the four factors that contribute to biventricular output: heart rate, contractility, preload, and afterload. Because we used pancuronium bromide during transfusions to effect fetal neuromuscular blockade, one might argue that any cardiac effect of this drug would influence the outcome of our study. Human neonatal studies indicate that pancuronium elevates heart rate by increasing catecholamine levels.[17] Pielet et al.[18] failed to show an elevation in fetal heart rate after intrauterine transfusions in which pancuronium was used for fetal paralysis. In our series we were also unable to detect an increase in the fetal heart rate after intrauterine transfusion. The most likely explanation for these findings is that the cardioacceleratory effects of pancuronium are transitory and had abated before posttransfusion cardiac measurements were performed. In a series of 14 fetuses undergoing intravascular transfusions in which only maternal sedation was used to decrease fetal movement, Pielet and coworkers[18] noted a decline in fetal heart rate from a baseline value of 137.1 ± 3.6 to 127.9 ± 14.6 beats/min after transfusion. Although this difference did not reach statistical significance, it suggests that the fetal cardiovascular system may respond to the acute correction of anemia by a decrease in heart rate. In our study, pancuronium could have blocked such a decline in heart rate after transfusion. For this reason, the decrease in fetal cardiac output that we observed may be an underestimation of the actual fall after intrauterine transfusion. However, because an alteration in heart rate was not detected in the current study, another explanation for the decline in cardiac output must be postulated.

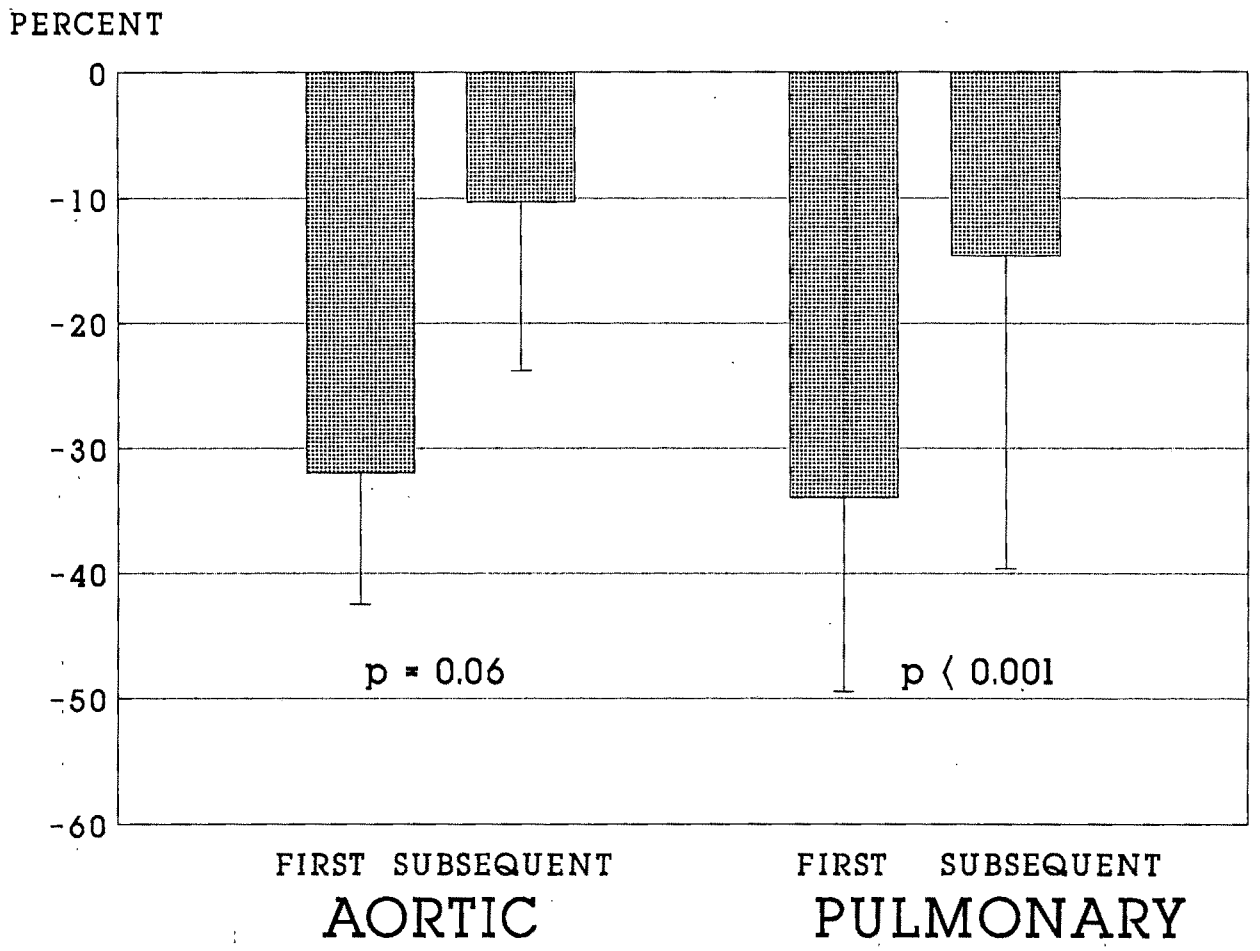


Fig. 6. Percent change in left and right ventricular output (time velocity integral × heart rate) at first transfusions as compared with subsequent procedures (mean ± SD).

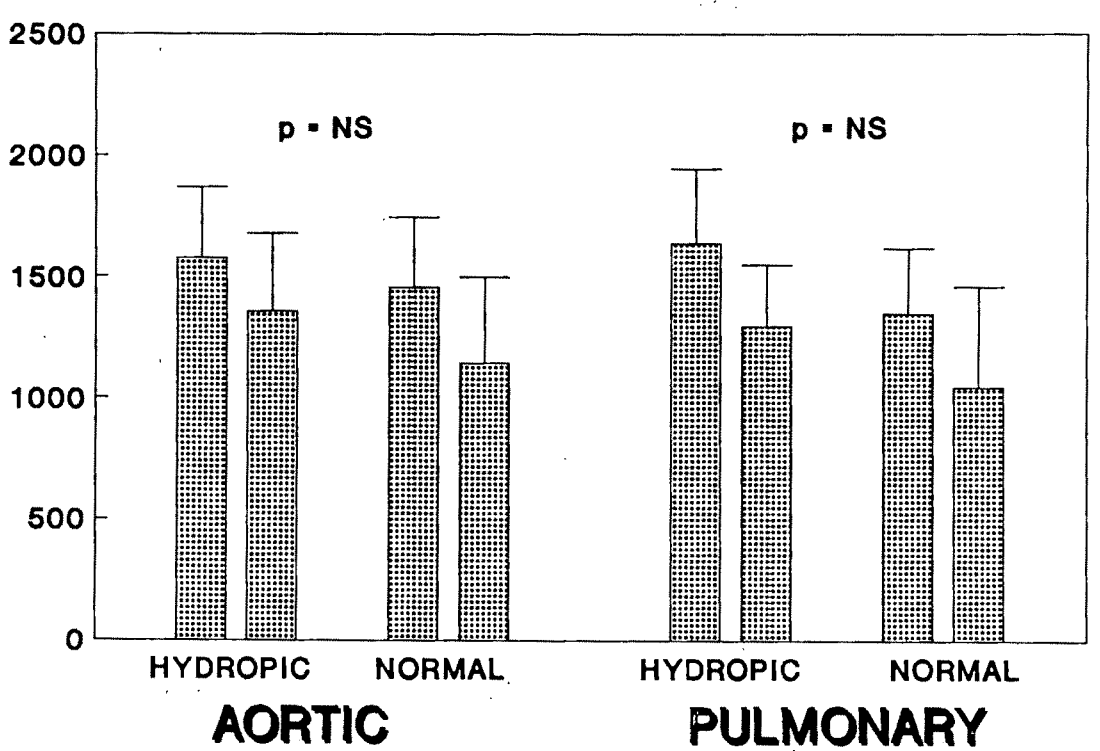


Fig. 7. Percent change in left and right ventricular output (time velocity integral × heart rate) for hydropic fetuses versus nonhydropic fetuses (mean ± SD).

If intravascular transfusion resulted in a decrease in myocardial contractility, cardiac output would be expected to decline. With mean acceleration as a measure of myocardial function, we could not detect a significant change after transfusion. This would lead us to conclude that factors other than myocardial dysfunction contributed to the observed decrease in fetal cardiac output.

In the current study, intravascular transfusion resulted in a calculated mean increase in the fetoplacental volume of 18%. In addition, umbilical venous pressure increased by a mean of 1.7 mm Hg. These findings would lead us to conclude that intravascular transfusion produced an increase in cardiac preload. Such a change in preload would be expected to effect an increase in cardiac output, or at best, produce no change at all. Available information from animal studies indicates that the fetal heart is functioning near the upper end of the Starling curve.[19] If this is true in the human fetus, one would expect no change or a small increase in ventricular output with the addition of volume to the fetal vascular space. However, we found a decline in cardiac output in our series of fetuses. We used a combined transfusion technique that consisted of the direct intravascular injection of red cells through the umbilical vein followed by a standard intraperitoneal transfusion. Nicolini and coworkers[7] reported that intraperitoneal pressure increases by a mean of 5.8 mm Hg after intraperitoneal transfusion. Therefore, although intravascular volume was increased in our fetuses, a rise in intraperitoneal pressure could have decreased venous return to the fetal heart. This might explain the fall in cardiac output noted in our study.

However, an increase in cardiac afterload would appear to offer the best explanation for the decrease in cardiac output that we noted. In two studies in the ovine fetus,[20, 21] the rapid intravascular injection of tightly packed red blood cells (hematocrit of ≥70%) produced substantial increases in mean arterial pressure. A similar rise in blood pressure in the human fetus in conjunction with the fall in cardiac output that we observed would suggest that systemic vascular resistance increased in our fetuses. In animal experiments, Fan et al.[1] noted that a progressive increase in hematocrit induced by isovolemic transfusion was associated with an increase in systemic resistance. Blood viscosity measurements revealed that this parameter may play a role in the observed increase in peripheral resistance.[1] Direct intravascular transfusion would therefore appear to result in an increase in cardiac afterload, possibly through an increase in blood viscosity. The fetal heart responds to the increased afterload by a decrease in stroke volume leading to a fall in cardiac output.

Unlike the current study, Copel et al.[6] did not find a change in cardiac output after intravascular transfusion of the human fetus. This difference may be related to the time interval before measurement of the posttransfusion cardiac output. In our study, Doppler assessment of cardiac output was undertaken within 1 hour after transfusion, whereas Copel studied his fetuses 24 hours later. These findings may indicate that hemodynamic changes occur in the human fetus during the first 24 hours after direct intravascular transfusion to allow for resolution of the decreased cardiac output that occurs immediately after the procedure. Whether this initial decrease in cardiac output is a pathologic consequence of intravascular transfusion or whether it represents a normalization of cardiac output as a result of increased oxygen delivery to peripheral tissues requires further investigation. In addition, other studies appear warranted to determine whether the decline in cardiac output is unique to the combined intravascular-intraperitoneal technique of transfusion or whether it occurs after direct transfusion alone.

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Postinjection kinetics of antepartum Rh immune globulin

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The disappearance kinetics of a standard dose of 300 μg of Rh immune globulin given at 28 weeks' gestation was investigated. Ten Rh-negative unsensitized women were given 300 μg of Rh immune globulin at 28 weeks and blood samples were drawn at weekly intervals until delivery. Sera were titrated with Ror red blood cells in a saline solution–antiglobulin method. Titers ranged from 1 to 4 by the first week after injection. In nine of 10 patients the titers were zero at 49 to 70 days after injection. With R_2R_2 red blood cells and LISS, papain, polybrene, or a combination of methods, Rh immune globulin could still be detected until delivery in four of the nine patients. Because these serologic methods can detect 5 ng/ml anti-D, five of 10 subjects may not have been protected for 8 to 29 days before delivery. This study indicates that a titer of ≤4 is expected for passively acquired anti-D during pregnancy, and that antepartum administration of Rh immune globulin may not always produce detectable passive antibody for as long as theoretically predicted. (AM J OBSTET GYNECOL 1990;163:784-6.)

Key words: Rh sensitization, Rh disease, erythroblastosis fetalis, Rh hemolytic disease

The administration of 300 μg of Rh immune globulin at 28 to 29 weeks' gestation to unsensitized Rh-negative mothers is the common practice in the United States. This practice is based on pioneering studies by Boman et al.[1] In the first study, 300 μg of Rh immune globulin was administered at 28 and 34 weeks to 1204 women who ultimately were delivered of Rh-positive infants. No woman became sensitized, although historically 21 would have been expected to have been sensitized with only postpartum prophylaxis. On the basis of a theoretical calculation based on the half-life of gamma globulin, it was expected that a single injection of 300 μg of Rh immune globulin at 28 weeks would provide protection for 12 weeks or 84 days. Therefore antepartum prophylaxis with a single injection at 28 weeks was implemented. After implementation of this program the incidence of Rh isoimmunization decreased from 3.5 per 1000 births at risk with only postpartum prophylaxis to 2.0 per 1000 births at risk with both antepartum and postpartum prophylaxis.[2]

With consideration of the half-life of γ-globulin, a 300 μg dose of Rh immune globulin theoretically should result in a residual dose of 20 μg at 12 weeks after injection.[1] The level of residual Rh immune globulin is important because doses in the 10 to 20 μg range have been shown to actually enhance immunization of Rh-negative volunteers to similar small doses of Rh-positive cells.[3] However, enhancement has never been demonstrated in clinical practice.

This study was undertaken to determine if under clinical conditions, intramuscular administration of 300 μg of Rh immune globulin at 28 weeks' gestation does

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produce detectable passive antibody for 12 weeks or 84 days. In addition, we sought to determine the maximal titers of Rh immune globulin observed after injection.

Material and methods

After approval of this study by the Institutional Human Investigation Committee, we enrolled 10 informed, consenting, Rh-negative unsensitized pregnant women in this study. All women had Rh-positive male partners and were therefore at risk of carrying a Rh-positive fetus.

According to standard clinical practice, each woman received 300 μg of Rh immune globulin at 28 to 29 weeks' gestation by intramuscular injection in the deltoid muscle. Before injection all women were documented by antibody screening tests to be unsensitized to the Rh antigen. After injection titers were drawn at weekly intervals until delivery. The serum samples were stored frozen at −40° C until all samples from each subject were collected. Samples from each subject were then titrated in parallel by a standard saline solution–antiglobulin method.[4] The indicator red blood cells were from a D-heterozygous donor with Rh genotype Ror.

Samples that failed to react in titration studies were further tested for the presence of passive anti-D by use of more sensitive techniques that included the use of R_2R_2 indicator red cells and LISS, papain, or polybrene methods or a combination.[6]

The Rh immune globulin used for this study was provided by Rorer Pharmaceutical Corporation (Ft. Washington, Pa.). A single lot was used for subjects 1 through 9 and a second lot was used for subject 10. All Rh immune globulin was stored before use as specified by the package insert to maintain potency.

Results

All 10 subjects were documented to have no endogenous anti-D before Rh immune globulin administration. After injection all subjects demonstrated anti-D at titers of 1 to 4 within the first week. Titers between 1 and 2 persisted in all subjects through 42 days after injection. Subject four was delivered at 56 days after injection with a positive titer of 1. The other subjects' titers decreased to zero before delivery at 49 to 70 days after administration of Rh immune globulin (Table I).

Samples from the nine subjects who had no demonstrable anti-D before delivery in titration studies were further tested with more sensitive techniques. Four subjects had demonstrable antenatal Rh immune globulin until delivery, whereas in five subjects no anti-D could be demonstrated as early as 55 days after injection. Table II lists the days after injection until the first undetectable sample or delivery for the nine subjects with Rh titers of zero before delivery. Thus, half the subjects in this study were without detectable Rh immune globulin levels for 8 to 29 days before delivery (Table III).

Table I. Time after injection when Rh immune globulin titer reached zero

No. of subjects	*Days after injection*
1	49
5	56
2	63
1	70

Table II. Detection of antenatal Rh immune globulin

Subject no.	*Days after injection*	*R_2R_2 (LISS, papain, polybrene)*
1	64	0
2	70	0
3	71	+
5	69	0
6	63	+
7	77	+
8	55	0
9	57	0
10	68	+

Table III. Time without detectable anti-D before delivery

Subject no.	*Days before delivery*	*Infant Rh type*
1	27	+
2	8	+
5	15	0
8	29	+
9	27	0

Comment

The absence of detectable anti-D by our more sensitive serologic methods in 50% of our subjects for 8 to 29 days before delivery is not consistent with the presence of 20 μg of Rh immune globulin at 84 days after injection as predicted by the theoretical half-life of gamma globulin. Our more sensitive serologic methods can detect <0.005 μg/ml of anti-D. If 20 μg of anti-D were present, given the mean plasma volume of our subjects of 3400 ml, the anti-D concentration in the sera should have been 0.006 μg/ml and therefore would have been detectable by our methods.

Commercially available Rh immune globulin was used in this study. Food and Drug Administration standards require at least 300 μg to be present; however, a 300 μg dose may contain slightly more than 300 μg. This possible variation in the amount of Rh immune globulin might account for some variability in the

disappearance of antepartum Rh immune globulin. Its effect should have been to lengthen the time to disappearance from that theoretically predicted for 300 μg.

No subject in the study had antepartum bleeding. We had no clinical reason to suspect that fetal-maternal bleeding could account for the disappearance of the anti-D antibody, and two of the subjects without detectable Rh immune globulin had Rh-negative fetuses. We therefore believe that these are valid findings representing variations in the biologic half-life of Rh immune globulin. This variation in the biologic half-life of Rh immune globulin is not unique to the anti-D preparation that we studied. In applying our sensitive serologic assays to samples taken at delivery from patients known to have been injected with Rh immune globulin from two other manufacturers at less than 84 days before delivery, we found from 40% to 90% of the patients were without detectable anti-D levels.

The rate of sensitization with postpartum Rh immune globulin alone has been shown to be 3.5/1000 births at risk.[2] With the addition of a single antepartum injection of Rh immune globulin at 28 weeks the rate of sensitization can be lowered to 2.0/1000 births at risk.[2] In the original antepartum prophylaxis study by Boman et al.[1] in which 300 μg of Rh immune globulin was administered at 28 and 34 weeks, no sensitizations were found. Because of the rarity of antepartum sensitization the difference in sensitization rates between one and two doses of antepartum Rh immune globulin may be a result of sampling error. However, it would appear from our data that administration of 300 μg of antepartum Rh immune globulin may not always produce detectable passive antibody for 84 days and that rare sensitizations may be a result of early disappearance of antepartum Rh immune globulin.

Finally, a dose of 300 μg of Rh immune globulin should not be expected to produce a titer >4. Therefore in clinical practice the upper limit for passively acquired anti-D titers should be 4.

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Magnesium sulfate and promethazine do not interact to cause hypotension in gravid ewes

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The purpose of this study was to determine whether magnesium sulfate and promethazine interact to cause hypotension in gravid ewes. Fifteen experiments were performed in five chronicaly instrumented animals between 125 and 130 days of timed gestation (term = 145 days). In one group of experiments each animal received magnesium sulfate (4 gm intravenous bolus followed by 4 gm/hr intravenous infusion) then promethazine (50 mg intravenously). In a second group each animal received magnesium sulfate then saline solution as a control. In a third group each animal received saline solution then promethazine. Infusion of magnesium sulfate increased the mean (±SEM) serum magnesium concentration to 5.7 ± 0.6 and 6.6 ± 0.6 mg/dl in the magnesium sulfate–promethazine and magnesium sulfate—saline solution groups, respectively. Magnesium sulfate slightly decreased maternal mean arterial pressure ($p < 0.05$) and increased cardiac output ($p < 0.05$) in both the magnesium sulfate–promethazine and magnesium sulfate–saline solution groups. Otherwise there were no significant changes in maternal mean arterial pressure or cardiac output in any group. Promethazine increased maternal heart rate ($p = 0.0001$) in both the magnesium sulfate–promethazine and saline solution–promethazine groups. Magnesium sulfate increased uterine blood flow ($p < 0.01$) in both the magnesium sulfate–promethazine and magnesium sulfate–saline solution groups, but promethazine blunted the increase in uterine blood flow associated with magnesium sulfate. Similarly, magnesium sulfate decreased uterine vascular resistance ($p < 0.01$) in both the magnesium sulfate–promethazine and magnesium sulfate-saline solution groups, but promethazine eliminated the decrease in uterine vascular resistance associated with magnesium sulfate. Maternal and fetal arterial blood gas and acid-base values did not change in any group, except that there was a small, near-significant decrease ($p = 0.06$) in fetal pH 10 minutes after promethazine was given in the magnesium sulfate–promethazine group. We conclude that magnesium sulfate and promethazine did not interact to cause maternal hypotension in normovolemic gravid ewes. However, promethazine increased maternal heart rate and blunted the increase in uterine blood flow associated with magnesium sulfate. (Am J Obstet Gynecol 1990;163:787-94.)

Key words: Magnesium sulfate; phenothiazines, promethazine; pregnancy

Promethazine is a phenothiazine that possesses antiemetic, antihistaminic, and sedative properties. Magnesium sulfate is frequently used for seizure prophylaxis in preeclampsia and for tocolysis in preterm labor. A common side effect of magnesium sulfate is nausea. Some obstetricians give promethazine to treat the nausea associated with magnesium sulfate therapy. Bourgeois et al.[1] observed profound hypotension in two women with preeclampsia who received both magnesium sulfate and promethazine 25 mg intravenously. Frohlich[2] subsequently suggested that an interaction between magnesium sulfate and promethazine may have been responsible for the hypotension. He asserted that promethazine, through its inhibition of phosphodiesterase and calmodulin, might cause hypotension when it is administered with magnesium sulfate. (Inhibition of phosphodiesterase can cause vasodilation via an increase in β-adrenergic activity.[3, 4] Calmodulin inhibition can cause hypotension by direct relaxation of vascular smooth muscle.[5]) Magnesium sulfate also inhibits calmodulin and is a direct calcium antagonist.[6] Therefore magnesium sulfate and promethazine might have a synergistic effect on vascular smooth muscle tone and thereby cause profound hypotension. The purpose of this study was to determine whether magnesium sulfate and promethazine interact to cause maternal hypotension in gravid ewes.

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Material and methods

The protocol was approved by the University of Iowa Animal Care Committee. Mixed breed ewes were obtained at approximately 118 days of timed gestation

(term = 145 days). Each animal fasted for 36 hours before operation. At 120 days' gestation induction of general anesthesia was accomplished with thiopental sodium (8 to 12 mg/kg). After tracheal intubation anesthesia was maintained with 40% nitrous oxide, 60% oxygen, and 1% to 1.5% halothane. Mechanical ventilation was maintained throughout operation. With sterile technique laparotomy and hysterotomy were performed, and catheters (polyethylene 90) were inserted into the fetal descending aorta via each femoral artery and into the amniotic cavity. After the hysterotomy and laparotomy incisions were closed, a left paramedian incision was made. The left uterine artery was isolated via a retroperitoneal approach, and an electromagnetic flow probe (Dienco, Los Angeles) was placed around the artery. Catheters (polyethylene 240) were then inserted into the maternal descending aorta and inferior vena cava via the left mammary artery and vein, respectively. All catheters were tunneled subcutaneously and exteriorized through a small incision in the left flank. Finally, an Fr. 8.5 introducer (AK09800, Arrow, Reading, Pa.) was inserted percutaneously into the right jugular vein.

After operation each animal was kept in an approved cage in a restricted area, fed a balanced diet, and allowed a recovery period of at least 5 days. Procaine penicillin G 500,000 U and dihydrostreptomycin 625 mg (Combiotic, Pfizer, New York) were given to the mother intramuscularly before operation and daily for 3 days after operation. Gentamicin 80 mg was given to the mother intravenously the day of each experiment, and gentamicin 40 mg was given via amniotic catheter during operation and the day of each experiment.

Each experiment was performed with the animal standing unrestrained within an approved transport cart. Before the first experiment in each animal, a pulmonary artery catheter (No. 93A-131H-7F, American Edwards Laboratories, Santa Ana, Calif.) was inserted through the jugular vein introducer. At the end of each experiment the catheter was withdrawn into the superior vena cava, and sterility was maintained with an 80 cm sheath.

The experimental sequence was as follows:

1. Hydration with 250 ml normal saline solution intravenously over 15 minutes.
2. One hour was allowed for baseline measurements.
3. At time zero a 50 ml intravenous bolus was given over 5 minutes (either 4 gm magnesium sulfate in saline solution or saline solution alone).
4. At 5 minutes an intravenous infusion of magnesium sulfate (4 mg/hr) in saline solution or saline solution alone was given. The total volume of crystalloid infused was 100 ml/hr in each group.
5. At 120 minutes a 20 ml intravenous bolus was given over 2 minutes (either promethazine 50 mg in saline solution or saline solution alone).

The infusion of magnesium sulfate (or saline solution alone) was continued through 180 minutes. Hemodynamic measurements were continued through 210 minutes.

Fifteen experiments were performed in five chronically instrumented gravid ewes. There were three experimental groups. In one group (magnesium sulfate–promethazine) each animal received magnesium sulfate then promethazine. In a second group (magnesium sulfate–saline solution) each animal received magnesium sulfate then saline solution. In a third group (saline solution–promethazine) each animal received saline solution then promethazine. All three experiments were performed on each animal, in random order. Only one experiment was performed per day, and each animal rested at least 24 hours between experiments.

Maternal arterial blood pressure, central venous pressure, pulmonary artery pressure, and fetal arterial blood pressure were measured continuously via disposable strain gauge pressure transducers (No. 46951-02, Abbott Critical Care Systems, North Chicago). Fetal pressures were corrected by subtraction of simultaneous intraamniotic pressure. Mean arterial blood pressure was computed arithmetically. The maternal heart rate and fetal heart rate were computed from the arterial waveforms. Uterine artery blood flow was measured continuously with a quantitative electromagnetic flowmeter (No. RF-2500, Dienco, Los Angeles) in three of five animals (i.e., nine of 15 experiments). Arterial and venous pressures, heart rates, and uterine artery blood flow were recorded at 10-second intervals with a customized data acquisition system (Coulbourn Instruments, Lehigh Valley, Pa.) interfaced with a personal computer (PCXT, IBM, Rochester, Minn.).

Maternal cardiac output was determined at baseline and at 10, 120, 130, 180, and 210 minutes. Measurements were made in triplicate with 10 ml of iced saline solution and a thermodilution cardiac output computer (No. 9520, American Edwards Laboratories).

Maternal and fetal arterial blood gas and pH values were determined at baseline and at 120, 130, 180, and 210 minutes with an Instrumentation Laboratory (No. 1302, Leighton, Mass.) blood gas analyzer. All values were corrected for temperature. Maternal serum magnesium concentrations were determined at baseline and at 10, 120, 130, 180, and 210 minutes by a bichromatic colorimetric assay.

Statistical analysis was by three-factor analysis of variance, followed by t tests for individual measurements.

Bonferroni correction was applied as appropriate. A value of $p < 0.05$ was considered significant.

Results

The mean (±SEM) weight of the animals was 66 ± 4 kg. Baseline maternal and fetal hemodynamic, blood gas, and acid-base measurements were similar in the three groups (Tables I and II). Magnesium sulfate administration caused similar increases in maternal serum magnesium concentrations in the magnesium sulfate–promethazine and magnesium sulfate–saline solution groups. At 120 minutes mean (±SEM) serum magnesium concentrations were 5.7 ± 0.6 mg/dl in the magnesium sulfate–promethazine group and 6.6 ± 0.6 mg/dl in the magnesium sulfate–saline solution group. (These concentrations were within the therapeutic range for seizure prophylaxis[7, 8] and tocolysis[9, 10] in pregnant women.) Serum magnesium concentrations did not change in the saline solution–promethazine group.

At 10 minutes magnesium sulfate slightly decreased maternal mean arterial pressure ($p < 0.05$) in both the magnesium sulfate–promethazine and magnesium sulfate–saline solution groups (Fig. 1). At no other time did maternal mean arterial pressure significantly differ from baseline in any group. Specifically, there was no significant change in maternal mean arterial pressure after promethazine administration in either the magnesium sulfate–promethazine group or the saline solution—promethazine group.

Magnesium sulfate did not significantly alter maternal heart rate (Fig. 2). Promethazine increased maternal heart rate ($p = 0.0001$) in both the magnesium sulfate–promethazine and saline solution–promethazine groups. Maternal heart rate remained stable within the magnesium sulfate–saline solution group.

Maternal central venous pressure and pulmonary capillary wedge pressure did not change significantly in any group. At 10 minutes magnesium sulfate slightly increased maternal cardiac output ($p < 0.05$) in both magnesium sulfate–promethazine and magnesium sulfate–saline solution groups (Fig. 3). At no other time did maternal cardiac output significantly differ from baseline in any group.

At 120 minutes magnesium sulfate had increased uterine blood flow to 120% ± 5% of baseline ($p = 0.005$) in the magnesium sulfate–promethazine group and to 122% ± 4% of baseline ($p = 0.002$) in the magnesium sulfate–saline solution group (Fig. 4). Uterine blood flow remained significantly greater than baseline until the completion of the experiment in the magnesium sulfate–saline solution group. In contrast, promethazine blunted the increase in uterine blood flow in the magnesium sulfate–promethazine group. Uterine blood flow did not change singificantly in the saline solution–promethazine group.

Magnesium sulfate decreased uterine vascular resistance ($p < 0.01$) at 10 and 120 minutes in both the magnesium sulfate–promethazine and the magnesium sulfate–saline solution groups (Fig. 5). Uterine vascular resistance remained significantly below baseline

Table I. Baseline maternal hemodynamic, acid-base, and blood gas measurements

	Magnesium sulfate–promethazine	*Magnesium sulfate–saline solution*	*Saline solution–promethazine*
Mean arterial pressure (mm Hg)	92 ± 3	93 ± 2	95 ± 3
Central venous pressure (mm Hg)	3 ± 2	3 ± 2	4 ± 1
Pulmonary wedge pressure (mm Hg)	7 ± 1	8 ± 2	8 ± 2
Heart rate (beats/min)	102 ± 7	109 ± 3	109 ± 3
Cardiac output (L/min)	8.2 ± 0.9	8.3 ± 1.3	9.6 ± 1.2
Uterine blood flow (ml/min)	553 ± 200	464 ± 108	500 ± 140
Intraamniotic pressure (mm Hg)	8 ± 3	6 ± 3	8 ± 1
Arterial pH	7.41 ± 0.02	7.42 ± 0.02	7.43 ± 0.02
Arterial P_{O_2} (mm Hg)	104 ± 3	105 ± 3	102 ± 5
Arterial P_{CO_2} (mm Hg)	37 ± 1	37 ± 1	37 ± 0.4
Serum magnesium (mg/dl)	1.4 ± 0.1	1.2 ± 0.1	1.4 ± 0.1

All values are expressed as mean ± SEM.

Table II. Baseline fetal hemodynamic, acid-base, and blood gas measurements

	Magnesium sulfate–promethazine	*Magnesium sulfate–saline solution*	*Saline solution–promethazine*
Mean arterial pressure (mm Hg)	43 ± 3	45 ± 3	46 ± 4
Heart rate (beats/min)	169 ± 7	165 ± 11	152 ± 14
Arterial pH	7.34 ± 0.004	7.34 ± 0.01	7.35 ± 0.01
Arterial P_{O_2} (mm Hg)	20 ± 1	20 ± 1	21 ± 1
Arterial P_{CO_2} (mm Hg)	48 ± 2	48 ± 1	48 ± 2

All values are expressed as mean ± SEM.

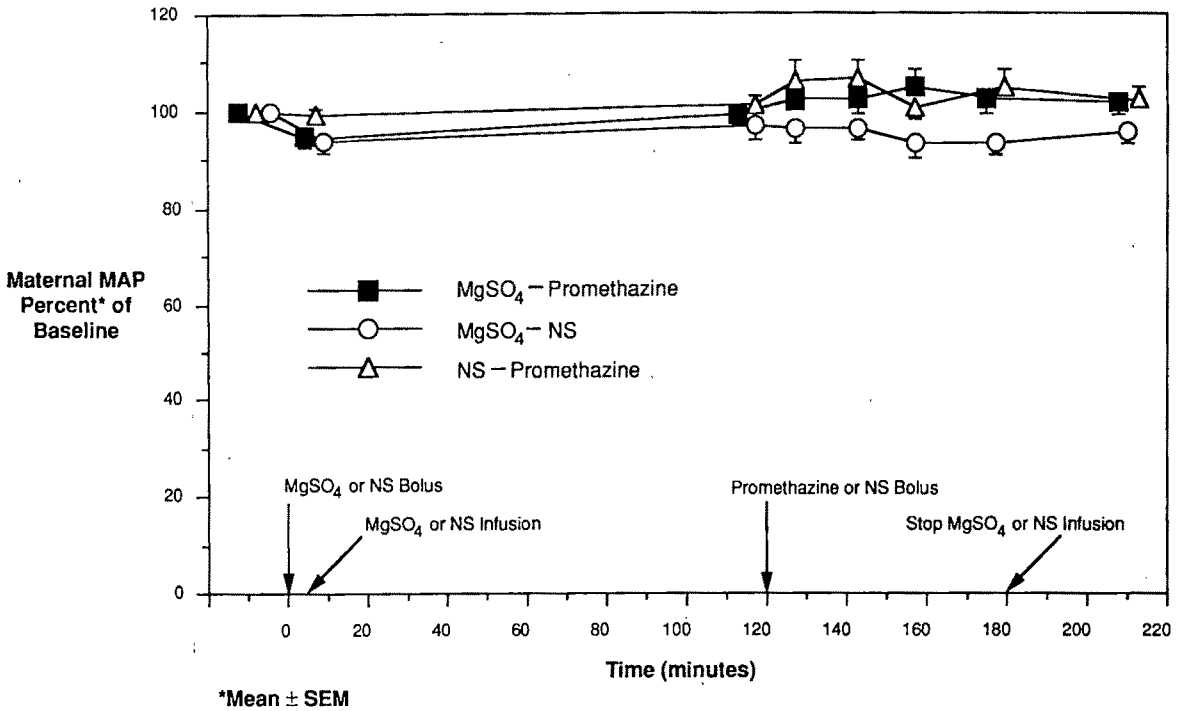


Fig. 1. Maternal mean arterial pressure *(AMP)* responses over time. All values are expressed as mean ± SEM. Magnesium sulfate decreased maternal mean arterial pressure ($p < 0.05$) at 10 minutes in both the magnesium sulfate–promethazine and magnesium sulfate–saline solution groups.

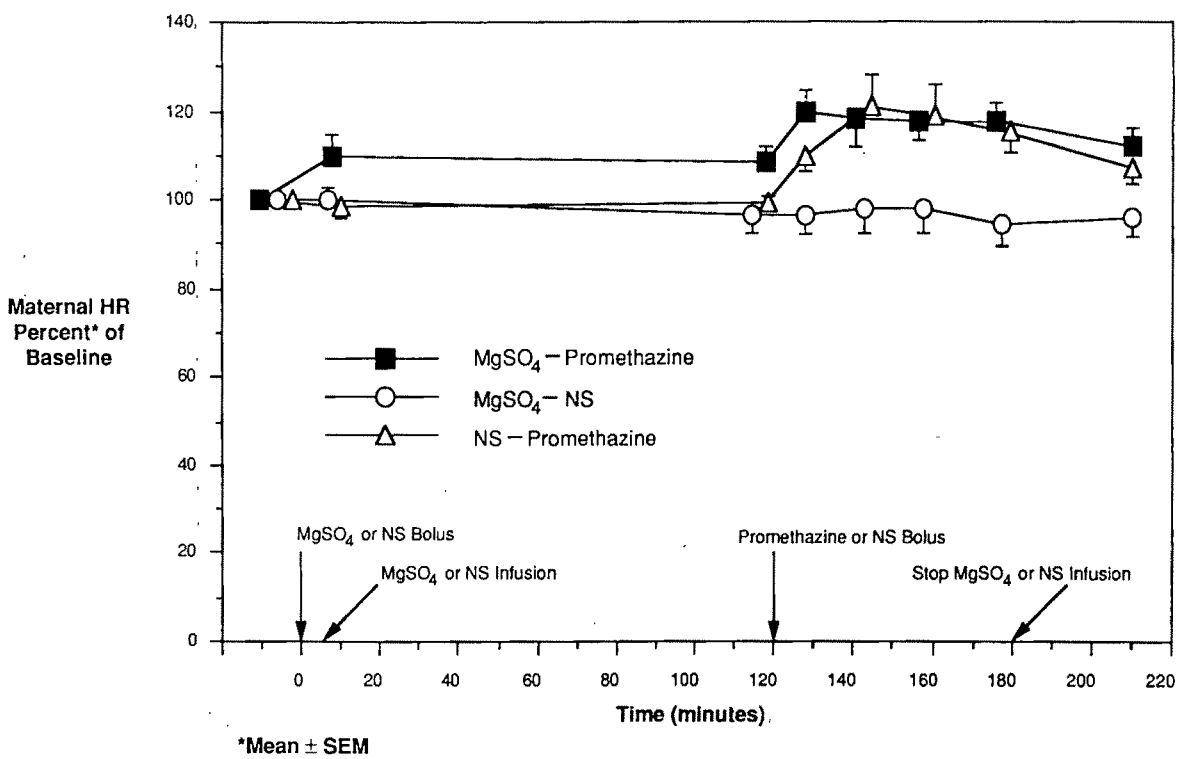


Fig. 2. Maternal heart rate *(HR)* responses over time. All values are expressed as mean ± SEM. There was a significant increase in maternal heart rate ($p < 0.01$) at each measurement between 130 and 210 minutes in the magnesium sulfate–promethazine group and between 130 and 180 minutes in the saline solution–promethazine group.

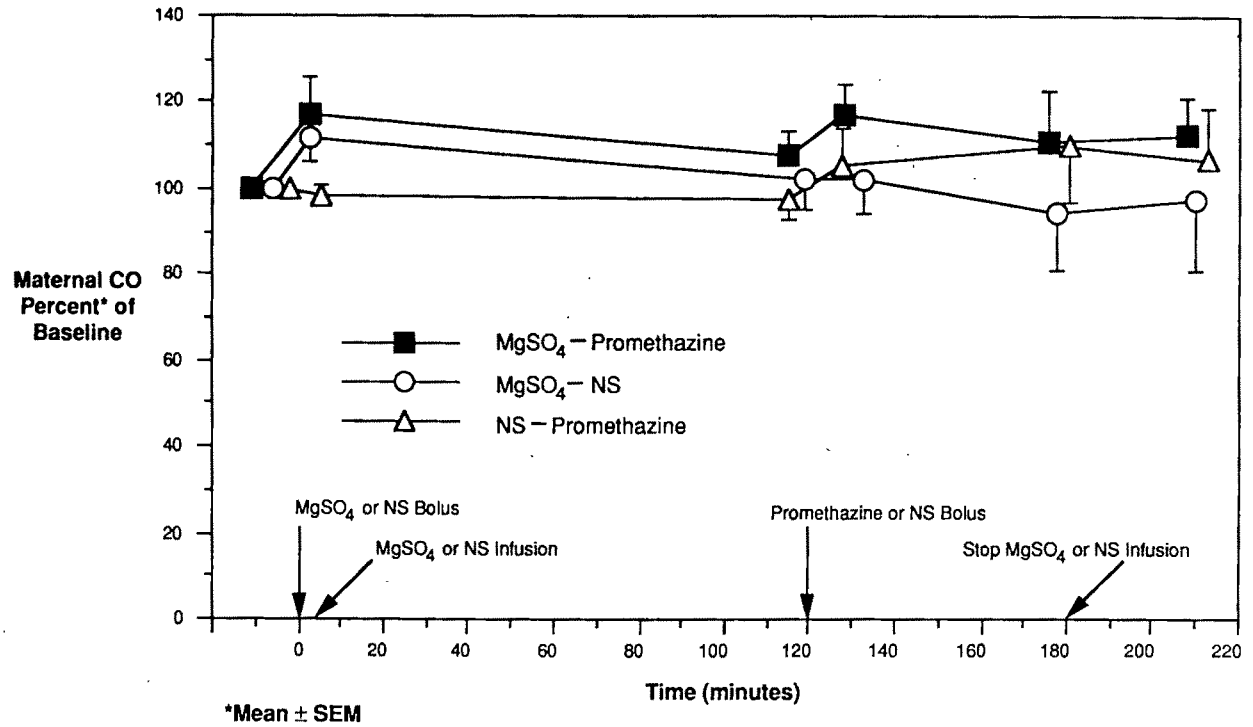


Fig. 3. Maternal cardiac output *(CO)* responses over time. All values are expressed as mean ± SEM. There was a significant increase in maternal cardiac output ($p < 0.05$) at 10 minutes in both the magnesium sulfate–promethazine and magnesium sulfate–saline solution groups.

until the completion of the experiment in the magnesium sulfate–saline solution group. In contrast, in the magnesium sulfate–promethazine group promethazine eliminated the decrease in uterine vascular resistance associated with magnesium sulfate. (Promethazine did not significantly alter systemic or pulmonary vascular resistance in either the magnesium sulfate–promethazine or saline solution–promethazine group.)

Magnesium sulfate decreased intraamniotic pressure ($p < 0.01$) in both the magnesium sulfate–promethazine and magnesium sulfate–saline solution groups. The addition of promethazine did not significantly alter intraamniotic pressure in either the magnesium sulfate–promethazine or saline solution–promethazine group. Thus the increase in uterine vascular resistance after promethazine did not result form an increase in uterine tone.

Maternal arterial pH, P_{O_2}, and P_{CO_2} did not change significantly in any group. Similarly, fetal heart rate, mean arterial pressure, and arterial P_{O_2} and P_{CO_2} did not change significantly in any group. However, there was a near-significant decrease ($p = 0.06$) in fetal pH at 130 minutes (i.e., 10 minutes after promethazine administration) in the magnesium sulfate–promethazine group (Fig. 6). The decrease in pH was small and resolved within 1 hour.

Comment

Several investigators have studied the hemodynamic effects of magnesium sulfate in gravid ewes. Dandavino et al.[11] and Ayromlooi et al.[12] observed small, transient decreases in maternal mean arterial pressure and increases in uterine blood flow shortly after administration of an intravenous bolus of magnesium sulfate. Similarly, in the present study magnesium sulfate decreased maternal mean arterial pressure 5% to 6% and increased uterine blood flow 20% to 22%. In addition, magnesium sulfate caused a transient increase in maternal cardiac output, which is consistent with earlier unpublished observations in gravid ewes.

In the present study the dose of magnesium sulfate (4 gm bolus and 4 gm/hr infusion) was similar to that used in other studies of gravid ewes.[11-13] Also, this dose of magnesium sulfate resulted in serum magnesium concentrations within the therapeutic range for seizure prophylaxis[7,8] and tocolysis[9,10] in pregnant women. We elected to give a 50 mg dose of promethazine. This is twice the dose that was administered to the patients reported by Bourgeois et al.[1] but within the range (i.e., 25 to 75 mg) used clinically.

Magnesium sulfate and promethazine did not interact to cause hypotension in the present study, but this does not prove that a drug interaction was not respon-

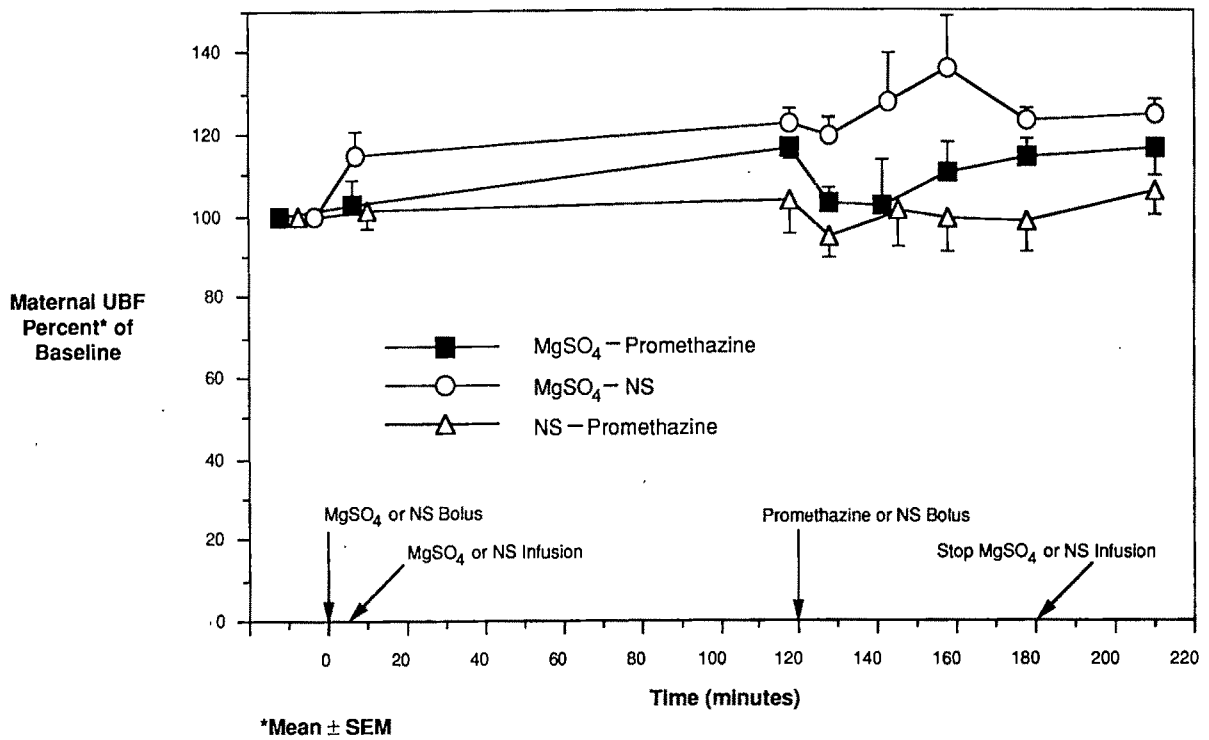


Fig. 4. Maternal uterine artery blood flow *(UBF)* responses over time. All values are expressed as mean ± SEM. There was a significant increase in maternal uterine blood flow at 10 and 120 minutes in the magnesium sulfate–promethazine group ($p = 0.005$) and at each measurement between 10 and 210 minutes in the magnesium sulfate–saline solution group ($p < 0.01$).

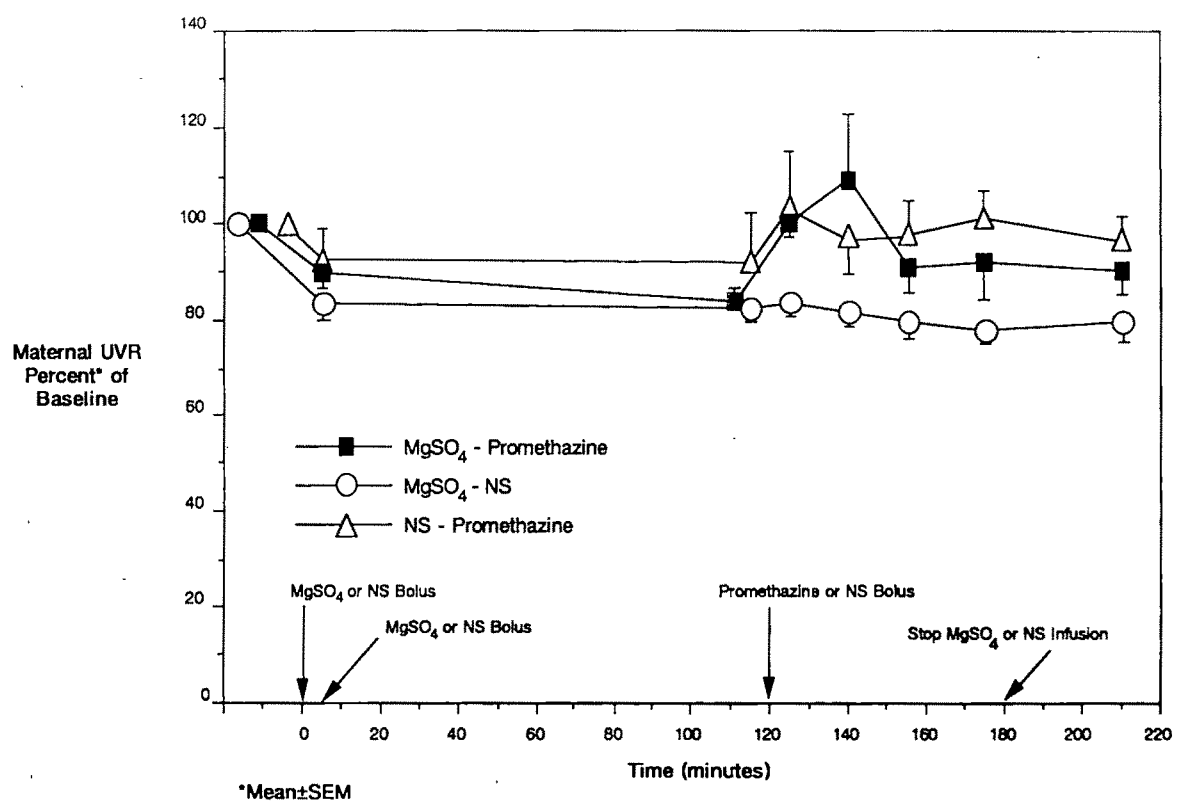


Fig. 5. Maternal uterine vascular resistance *(UVR)* responses over time. All values are expressed as mean ± SEM. There was a significant decrease in maternal uterine vascular resistance at 10 and 120 minutes in the magnesium sulfate–promethazine group ($p < 0.01$) and at each measurement between 10 and 210 minutes in the magnesium sulfate–saline solution group ($p < 0.01$).

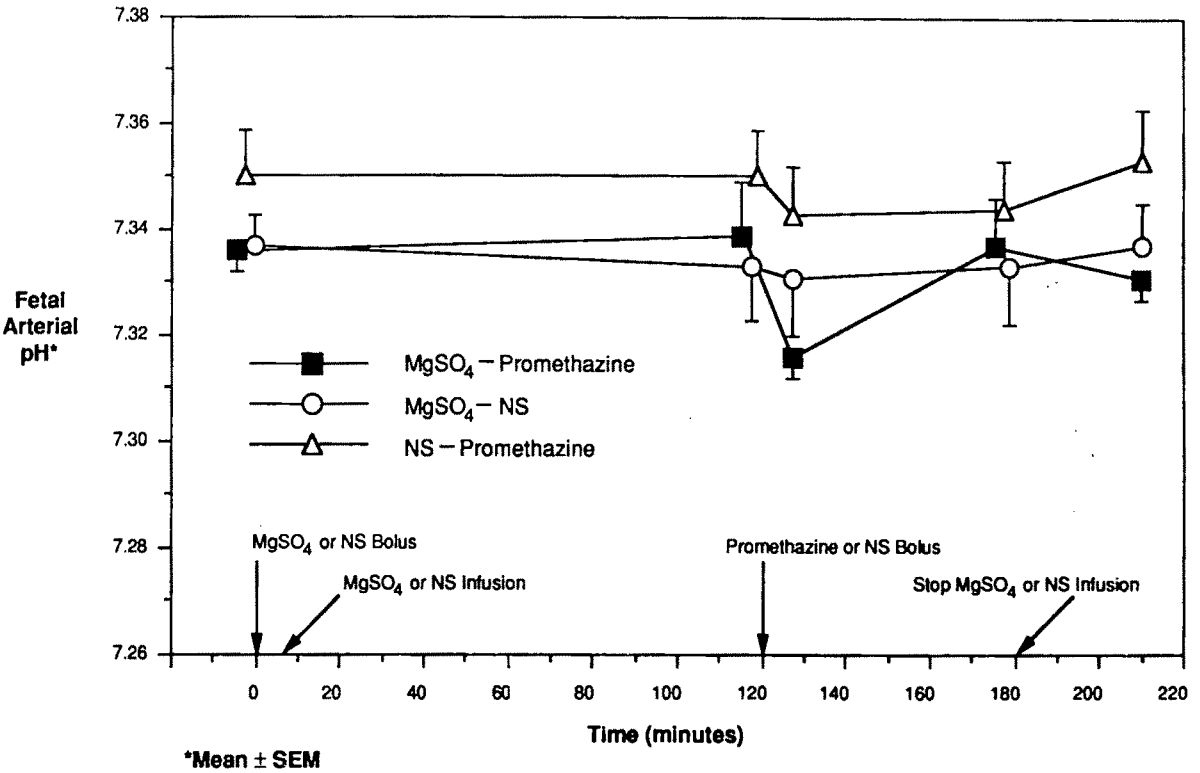


Fig. 6. Fetal arterial pH responses over time. All values are expressed as mean ± SEM. Fetal arterial pH decreased at 130 minutes in the magnesium sulfate–promethazine group ($p = 0.06$).

sible for the profound hypotension reported by Bourgeois et al.[1] First, we acknowledge the difference in species. Second, their two patients had preeclampsia and hypovolemia. In contrast, our animals were normovolemic before each experiment. (In the present study each animal received 250 ml of saline solution intravenously 1 hour before the start of each experiment). Third, magnesium sulfate and promethazine might have an adverse interaction in only a small percentage of animals or patients. Bourgeois et al.[1] stated that their patients frequently receive both magnesium sulfate and promethazine, yet profound hypotension was noted in only two patients.

While some believe that promethazine may exacerbate hypotension in the presence of hypovolemia, there is evidence to the contrary. Goetsch et al.[13] showed that administration of promethazine before hemorrhage improves both hemodynamic stability and survival in dogs. They speculated that the antihistaminic action of promethazine reduced vasodilation and thus raised blood pressure during hypovolemia.

It is interesting that promethazine increased uterine vascular resistance but had no significant effect on systemic and pulmonary vascular resistance, mean arterial pressure, or cardiac output. One possible explanation for this effect is that the anticholinergic effects of promethazine decreased the opposition to sympathetic tone. Elevated sympathetic tone is associated with increased uterine vascular resistance and decreased uterine blood flow in gravid ewes.[14, 15] Similarly, promethazine's anticholinergic properties may have resulted in the increased maternal heart rate observed in the present study.

We conclude that magnesium sulfate and promethazine did not interact to cause maternal hypotension in normovolemic gravid ewes. However, promethazine increased maternal heart rate and blunted the increase in uterine blood flow associated with magnesium sulfate. This interaction was associated with a small, transient decrease in fetal arterial pH. One must be cautious before extrapolating data from pregnant sheep to pregnant women. Further, one should not extrapolate these data to patients with preeclampsia and intravascular volume depletion. Nonetheless, this study suggests the need for further study of interactions between magnesium sulfate and phenothiazine drugs in pregnancy.

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Uterine hyperstimulation after low-dose prostaglandin E_2 therapy: Tocolytic treatment in 181 cases

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There is limited information about uterine hyperstimulation after low-dose prostaglandin E_2 therapy. The purpose of this retrospective study was to describe our combined experience with this undesired effect by use of three techniques for prostaglandin E_2 administration. Uterine hyperstimulation was present if the contraction frequency was more than five in 10 minutes or if contractions exceeded 2 minutes in duration. A total of 181 cases were evaluated during a 51-month period. The rates of hyperstimulation were 7.3% (167/2297) in the group that received intravaginal tablets (3.0 mg), 2.9% (12/408) with intravaginal gel (2.5 mg), and 0.5% (2/394) with intracervical gel (0.5 mg). Hyperstimulation usually began within the first hour for the group that used gel and within the first 4 hours for the tablet group. A β_2-adrenergic drug (hexoprenaline or terbutaline) was infused routinely without adverse effects and with rapid resolution of the worrisome findings in 178 (98.3%) cases. The remaining three cases required cesarean delivery and had no evidence of neonatal compromise. We conclude from this large, combined series that uterine hyperstimulation after low-dose prostaglandin E_2 therapy is uncommon and usually rapidly reversible with β_2-adrenergic therapy without apparent untoward effects. (AM J OBSTET GYNECOL 1990;163:794-6.)

Key words: Uterine hyperstimulation, prostaglandin E_2, cervical ripening

Many double-blind investigations have demonstrated the value of prostaglandin E_2 (PGE_2) for cervical ripening or induction of labor.[1] Although the primary aim of (PGE_2) therapy is often cervical ripening, uterine contractions occur coincidentally but are usually "silent" or mild. A major concern is the possibility of excess uterine activity leading to impaired uteroplacental perfusion.

The world literature contains only limited information about PGE_2-induced uterine hyperstimulation; such reports include either individual cases with relatively high doses or a small number of cases in comparative drug trials.[2-5] The purpose of this study was to report the combined experience at our two maternity centers. We reviewed the frequency of hyperstimulation associated with three methods of drug delivery

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(intravaginal tablet, intravaginal gel, intracervical gel) and described therapeutic results of β_2-adrenergic tocolytic therapy.

Material and methods

Cases at term (38 to 43 weeks) that required PGE_2 therapy before induction of labor were studied between January 1985 and March 1989. The pregnancies were not complicated by fever, vaginal bleeding, ruptured amniotic membranes, major fetal malformation, or known sensitivity to prostaglandins. The principal medical indications for cervical ripening included postdate pregnancies, hypertension, diabetes, and suspected fetal growth retardation.

Protocols before and after dosing were similar at the two maternity centers. Bishop scoring had been performed and a cervical score assigned in each case.[1] Prerequisites for PGE_2 therapy included a reassuring fetal heart rate (FHR) tracing (preferably a reactive nonstress test), informed patient consent, and absence of regular uterine contractions. Before treatment the upper vagina and cervix were swabbed free of any discharge or excess mucus.

Commercially available PGE_2 preparations in Vienna included a 3 mg vaginal tablet (Prostin E_2 vaginal tablet, Upjohn Ltd, Crawley, Sussex) and a 0.5 mg triacetin-based gel (Prepidil, Upjohn Ltd, Crawley, Sussex). According to protocol the gel was applied intracervically in cases of a cervical Bishop score of 0 to 3, whereas a tablet was inserted intravaginally when the Bishop score was between 4 and 6.[6] In Omaha a 2.5 mg cellulose-based gel was compounded in the hospital pharmacy and instilled intravaginally in cases of a cervical Bishop score of 0 to 4.[1]

All patients remained recumbent for at least 1 hour after PGE_2 administration with continuous electronic monitoring of the FHR and uterine activity. Monitoring was continued if regular uterine contractions developed. After a minimum 6-hour period the PGE_2 therapy was repeated if there was no labor or significant change in Bishop score ($\geq$3 points). Otherwise labor was induced with oxytocin beginning at 6 to 12 hours after dosing.

Uterine hyperstimulation was defined as a contraction frequency of more than five in 10 minutes or contractions exceeding a 2-minute duration.[7] For treatment of uterine hyperstimulation the patient was placed on her left side, given oxygen, and a β_2-adrenergic drug was administered. In Vienna hexoprenaline (Gynipral, Chemic Linz, Ling, Austria) was used intravenously starting at a rate of 0.3 μg/min, whereas in Omaha terbutaline (Brethine, Geigy, Ardsley, N.Y.) was administered as a single 250 μg dose intravenously or subcutaneously. Treatment was considered successful if contractions became less frequent with either reversal of any FHR decelerations or relief of any maternal discomfort. Continuous electronic monitoring occurred during active labor (cervical dilation $\geq$3 cm), and an amniotomy was performed as early as safely possible.

Results

Of a total of 3099 cases of low-dose PGE_2 therapy, 181 (5.8%) had evidence of uterine hyperstimulation during the 51-month period. Nulliparity was more common with stimulation (105/181, 58.0% vs 1188/2913, 40.7%; χ^2 21.7, p 0.001). Hyperstimulation occurred with similar frequency when the Bishop score was 4 to 6 compared with 0 to 3 (167/2860, 5.8% vs 14/239, 5.9%).

Hyperstimulation was observed in 7.3% (167/2297) of the group that received intravaginal tablets, 2.9% (12/408) of the intravaginal gel group, and 0.5% (2/394) of the intracervical gel group. This condition began after dosing within the first hour (24 ± 27 minutes, mean ± SD; range, 1 to 73 minutes) or within the first 4 hours in all intravaginal tablet cases.

Episodes of FHR abnormalities occurred in 31.5% (57/181) study cases. These patterns consisted of variable decelerations or bradycardiac episodes 1 to 5 minutes in duration. This finding was most common when contractions began and usually lasted throughout a recordable contraction.

Administration of a β_2-adrenergic drug was successful in normalizing uterine contractions and reversing any FHR abnormality in 178 (98.3%) cases. This normalization usually began within 5 minutes (range, 1 to 13 minutes) after tocolytic therapy regardless of the hyperstimulation pattern. Contractions persisted in three cases (one intravaginal gel, two intravaginal tablets) despite multiple doses of hexoprenaline or terbutaline. Although cesarean delivery was necessary in cases of persistent FHR decelerations, each infant did well with a 5-minute Apgar score $\geq$8 and umbilical artery pH value >7.20. The β_2-adrenergic therapy was not associated with any long-standing maternal cardiovascular side effects.

No intrapartum complications were attributable to PGE_2-induced uterine hyperstimulation. Any FHR abnormalities or uterine hypertonicity (failure of the uterus to relax between contractions or contractions in which the basal tone remained elevated for at least 2 minutes) appeared several hours after PGE_2 therapy. Cesarean delivery was necessary in 17 (9.4%) of the hyperstimulation cases for failure to progress (nine cases), fetal distress (six cases), and failed induction (two cases). Catastrophic side effects, such as a uterine rupture or amniotic fluid embolism, were not found.

Comment

PGE_2, a potent oxytocic agent, is helpful in changing cervical consistency and initiating labor. Nearly all patients would be expected to have mild uterine activity after the application of a low-dose of PGE_2 applied intracervically or intravaginally. Uterine contractions may be desirable if the goal is to ripen the cervix by myometrial contractions in addition to affecting cervical connective tissues.[4] Of much concern are excessive uterine contractions that became so frequent or sustained to warrant tocolytic therapy.

This descriptive study reports the experience with uterine hyperstimulation at two regional perinatal centers. Despite a heterogenous patient population, observations were combined to expand knowledge about this adverse effect with different PGE_2 preparations (0.5 mg intracervical gel, 2.5 mg intravaginal gel, 3.0 mg vaginal tablet). All three methods for drug delivery and dosing have been described previously, and our written protocols for predosing and postdosing monitoring were similar.

The incidence of uterine hyperstimulation in this investigation varied from 0.5% to 7.3%. A more favorable cervix (predose Bishop score of 4 to 6) or multiparity was not found to be contributory. Uterine hyperstimulation usually appeared within minutes after either intracervical or intravaginal gel application, because absorption velocities are rapid.[6] With tablets as a vehicle the lag time was prolonged up to 4 hours. The increased rate of hyperstimulation in the intravaginal tablet subgroups may be explained by the higher dose, different method of delivery, or closer proximity of the drug to the more fully exposed endocervical tissues. We consider our experience with use of intravaginal tablets to be clinically useful as more experience is being gained with use of PGE_2-containing intravaginal suppositories and pessaries.[6-8]

Observations from this noncomparative study also confirm the ease in reversing hyperstimulation with β_2-adrenergic therapy. Results from this large number of cases support previous impressions from isolated case reports or small series of patients. A description of other therapeutic measures is beyond the scope of this report but would include swabbing or irrigating the vagina or administering magnesium sulfate intravenously. Although these techniques may be helpful, administration of β-sympathomimetics has been described most commonly. Our limited experience with attempts at removing the gel has not been encouraging, and the use of intravenous magnesium sulfate is more time consuming and perhaps less rapid in normalizing uterine contractions.

We did not find intrapartum FHR patterns and uterine contractions to be influenced by any prior hyperstimulation. We have previously demonstrated by intrauterine pressure recordings that mothers given the 3 mg PGE_2 vaginal tablet had intrapartum uterine activities that were not statistically or clinically different from those of a control group with spontaneous labor.[9] Evidence for uterine hypertonicity during active labor was uncommon despite earlier hyperstimulation from PGE_2 therapy.

When low-dose PGE_2 is administered for cervical ripening or labor induction, close monitoring remains essential. This practice would permit tocolytic therapy to be instituted early to reverse any excessive PGE_2-induced contractions. Observations from this collective series revealed that uterine hyperstimulation after PGE_2 therapy is uncommon and can be rapidly reversed without apparent untoward intrapartum effects. β_2-Adrenergic therapy may be safely used to normalize excess uterine activity.

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Prevalence of use of cocaine and other substances in an obstetric population

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Increasing use of cocaine among pregnant women has been reported. This study was conducted to determine the prevalence of positive urine toxicologic screens for cocaine and other substances of patients admitted to the Sloane Hospital for Women. Urine samples were obtained from 509 women admitted to the delivery suite. The overall prevalence of cocaine was 10% (n = 51). Cocaine use was 10 times more prevalent in the clinic population (14%) than in the private population, (1.4%). In addition, women whose urine samples were positive for cocaine were more likely to have no prenatal care, previous induced abortions, to be human immunodeficiency virus–positive, and admitted previous use of cigarettes, alcohol, cocaine, and other drugs. Amphetamines were detected in 13% (n = 65) of patients. However, the screens did not distinguish between metabolites of amphetamines and other drugs such as cold medications. The medical history alone predicted only 37% (n = 19) of the cocaine-positive screens and none of the amphetamine-positive screens. (Am J Obstet Gynecol 1990;163:797-801.)

Key words: Cocaine, amphetamines, pregnancy, urine toxicologic screening

An escalation of cocaine use in the United States throughout the 1970s and 1980s has been well documented.[1] Significant adverse perinatal and neonatal effects of cocaine use in pregnancy have been reported including low birth weight, prematurity, abruptio placentae, and impaired neonatal behavioral assessment scores.[2-7] Studies in pregnant ewes have demonstrated significantly elevated maternal arterial pressure and decreased uterine blood flow during cocaine infusion, suggesting the pathophysiologic mechanisms that may cause these neonatal effects.[8, 9]

At the Sloane Hospital for Women in New York City the devastating effects of cocaine use are frequently observed in the obstetric and neonatal services. In a previous retrospective study we reviewed the results of all urine toxicologic screens sent from our labor room in 1987 and 1988. Cocaine was the drug most commonly identified. However, because of the selection of patients screened no conclusions regarding the prevalence of cocaine use could be made (data presented at Ninth Annual Meeting of Society of Perinatal Obstetricians, New Orleans, Louisiana, February 2-4, 1989, Abstract 79).

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Several studies have examined the prevalence of cocaine use in pregnant women.[10-12] These investigations, all conducted in large teaching hospitals, have identified prevalence rates from 8% to 17% in pregnant women. Because the pattern of drug abuse varies according to location and patient population, we surveyed urine toxicologic screens in the parturients to determine the prevalence of cocaine and other substance abuse.

Methods

This investigation was conducted from mid-November to Dec. 31, 1988, at the Sloane Hospital for Women. The study population included all women with pregnancies >20 weeks' gestation admitted consecutively to the labor suite for labor, premature rupture of membranes, or delivery by oxytocin induction or cesarean section. Routine urine samples were obtained for protein analysis. A portion was labeled with an anonymous numeric code, was frozen at −20° C and was stored for 2 to 4 months.

Demographic information, past medical and obstetric history, prenatal course, complications, and a record of all medications administered in the labor suite were obtained from the patient's medical record and labeled with the same numeric code. No informed consent was obtained because all data were recorded anonymously. This study was approved by the Institutional Review Board of the hospital.

The urine specimens were subsequently thawed and screened by enzyme immunoassay using EMIT reagents (Syva Corporation, Palo Alto, Calif.).[13] Urine was tested for the following drugs, their metabolities, or

Table I. Characteristics of study subjects

Characteristic	*Nonscreened**		*Screened†*		*p‡*
	n	%	*n*	%	
Total	105	100	509	100	
Age					
<18 yr	5	4.8	23	4.5	NS
18-25 yr	37	35	194	38	NS
>25 yr	63	60	292	58	NS
Service					
Private	39	37	145	29	NS
Clinic	66	63	362	71	NS
Ethnic group					
Hispanic	39	38	279	54	<0.05
Black	30	29	108	21	NS
White	32	31	102	20	<0.05
Multiparous	73	70	284	56	<0.01
Previous preterm	14	13	37	7.3	<0.05
No prenatal care	7	6.6	34	6.7	NS
History of substance use					
Cigarettes	17	16	63	12	NS
Alcohol	5	4.8	30	5.9	NS
Cocaine	6	5.7	24	4.7	NS

*Women for whom no urine was obtained for toxicologic screening.

†Women with urine toxicologic screens.

‡p value by χ^2 analysis.

both: cocaine, opiates, methadone, amphetamines, barbiturates, benzodiazepines, ethanol, and phencyclidine.

Urine samples were not available from all study patients because some were delivered too quickly or the specimen was inadvertently discarded. To determine the effect of this incomplete sampling, the same demographic and historical data were obtained on patients for whom no urine toxicologic screen was collected.

The data were analyzed with χ^2 analysis and t test when appropriate. Tests were considered statistically significant for values of $p < 0.05$. The Bonferroni correction was made when applicable.

Results

We obtained urine specimens and historical data for 509 women during the study period. At the same time we collected historical data but no urine specimen for 105 women. These two populations are compared in Table I. The patients for whom no urine was obtained (the nonscreened group) were more likely to be multiparous ($p < 0.01$) and to have had a previous preterm delivery ($p < 0.05$). There was also a higher percentage of white women and a lower percentage of Hispanic women in this group ($p < 0.05$). The nonscreened group contained a higher percentage of private patients compared with the study population, although this difference was not statistically significant. There were no differences in age, history of cigarette, alcohol, or cocaine use, or lack of prenatal care between these two groups.

Among the study patients 159 urine toxicologic screens were positive for drugs or their metabolites. In 36 patients this could have resulted from medications administered during the labor room stay; for example, opiates (meperidine) given during labor. These 36 patients were excluded from subsequent analysis. Thus 123 (24%) of all urine specimens studied were considered positive.

The distribution of drugs detected in the urine screens is shown in Table II. Cocaine or its metabolites and amphetamines were found in 10% ($n = 51$) and 13% ($n = 65$) of the population, respectively. Cocaine was found more commonly in the clinic population (14%, $n = 49$) than the private population (1.4%, $n = 2$). The detection of amphetamines in the two groups was similar: 14% ($n = 49$) in clinic patients and 11% ($n = 16$) in the private patients. All 13 patients found to have metabolites of marijuana in their urine were on the clinic service.

Cocaine was most likely to be detected alone ($n = 30$); when found with other drugs, cocaine was most often combined with marijuana ($n = 7$) or amphetamines ($n = 6$). Other substances infrequently ($n < 3$) detected with cocaine included opiates, barbiturates, methadone, and alcohol.

The demographic and historical information of women who had negative urine toxicology screens and those with positive tests for cocaine or amphetamines is shown in Table III. When the women with positive screening results for amphetamines were compared with the women whose results were negative for all substances, there was no statistically significant differ-

Table II. Results of urine toxicologic screens

Substance	All patients		Clinic patients		Private patients	
	n	%	*n*	%	*n*	%
n	509	100*	362	100	145	100
Total positive	123	24	102	28	21	14
Cocaine	51	10	49	14	2	1.4
Amphetamines	65	13	49	14	16	11
Marijuana	13	2.6	13	3.6	0	0
Opiates	5	0.9	4	1.1	1	0.7
Barbiturates	9	1.8	7	1.9	2	1.4
Methadone	1	0.2	1	0.3	0	0
Alcohol	5	0.9	3	0.8	2	1.4
Phencyclidine (PCP)	1	0.2	1	0.3	0	0

* For two patients the service was unknown.

Table III. Comparison of patients with negative urine toxicologic screens with women with positive screens for cocaine or amphetamines

Characteristic	Negative screens		Positive for cocaine		Positive for amphetamines	
	n	%	*n*	%	*n*	%
Total	350	100	51	100	65	100
Age group						
<18 wk	14	4.0	1	2.0	7	11
18-25 wk	139	40	22	43	21	32
>25 wk	197	56	28	55	37	57
Service						
Private	107	31	2	3.9*	16	25
Clinic	241	69	49	96*	49	75
Ethnic group						
Hispanic	197	56	30	59	36	55
Black	70	20	17	33	15	23
White	70	20	3	5.9	13	20
No prental care	15	4.3	15	29*	4	6.2
History of substance use						
Cigarettes	33	9.8	19	37*	8	12
Alcohol	15	4.5	11	22*	2	3.1
Cocaine	4	1.1	19	37*	2	3.1

*Different from patients with negative urine toxicologic screen ($p < 0.01$) by χ^2 analysis.

ence in age, service, ethnic group, parity, or use of other substances. However, women with positive tests for cocaine were less likely to be on the private service and more likely to have had no prenatal care than those with negative results for any drug ($p < 0.05$). There was no difference in parity or previous preterm deliveries in the two groups. However, 52% ($n = 27$) of women with positive tests for cocaine had previous induced pregnancy terminations compared with 29% ($n = 101$) in the negative group ($p < 0.01$). In addition, women in the cocaine-positive group were more likely to give a history of cigarette, alcohol, cocaine, or other drug use. There was a higher percentage of black women and a lower percentage of white women in the cocaine-positive group; however, these differences were not statistically significant. When the women with positive results for both cocaine and amphetamines were excluded from the analysis, the statistical significance of the comparisons was not altered.

Overall complications were higher among the women with positive cocaine tests (Table IV). Anemia was more common among the cocaine group compared with the patients with negative results ($p < 0.05$). This tendency was not seen in the amphetamine-positive group. Abruptio placentae was seen in 4% ($n = 2$) of women with positive tests for cocaine and in 1.4% ($n = 5$) among those with negative tests. These numbers are too small for statistical analysis. Three patients with known human immunodeficiency virus–positive results were delivered during the study period and all had screens positive for cocaine.

In the cocaine-positive group, more women were admitted for labor or rupture of membranes at less than 37 weeks' gestation compared with women who had

Table IV. Complications in women with negative urine toxicologic screens compared with women with positive screens for cocaine or amphetamines

Complication	*Negative screens (Total = 350)*		*Positive for cocaine (Total = 51)*		*Positive for amphetamines (Total = 65)*	
	n	%	*n*	%	*n*	%
Preterm labor	58	17	15	30*	5	7.1
Anemia	135	39	29	57*	30	46
PROM	36	10	7	13	3	4.6
Meconium	52	15	12	24	12	28
Preeclampsia	14	4.0	4	7.8	4	6.2
Abruptio placentae	5	1.4	2	3.9	0	0
Syphilis	8	0.3	6	11	1	1.5
HIV	0	0	3	5.9	0	0

PROM, Premature rupture of membranes; *HIV,* human immunodeficiency virus.
*Different from women with negative urine toxicologic screens ($p < 0.05$) by χ^2 analysis.

negative urine toxicology screens ($p < 0.05$). Several women who had positive test results for amphetamines received β-sympathomimetic medications for treatment of premature labor. Because metabolites of these drugs would be identified by the EMIT reagents as amphetamines, these patients were among those excluded from the analysis of the positive toxicology group. Therefore our data on premature labor in the amphetamine-positive patients cannot be interpreted.

In the entire screened population, 24 women gave a history of cocaine use alone or in combination with other drugs. The urine screens for four of these women were negative for any drugs. Cocaine alone or in combination with other drugs was detected in 19 patients; amphetamines were found in one. Three patients reported past use of drugs other than cocaine. Two of these had positive results for cocaine and one had a negative screen.

Comment

Cocaine use during pregnancy has reached epidemic proportions in inner-city populations.[10-12] Our data show that the prevalence of cocaine use in our clinic population is similar to that reported in other studies. Private patients had positive test results for cocaine use with less frequency.

Although we did not have toxicology screens performed for our entire population, the demographic analysis revealed no consistent differences between the screened and nonscreened groups. The higher parity among the latter suggests that they were delivered before a urine specimen could be obtained. Although there was a difference in ethnic distribution between the screened and nonscreened women, the two groups were similar with respect to all factors that were associated with cocaine use.

A surprising finding was the high prevalence of amphetamine use. Patients who had positive test results for amphetamines were clearly demographically different from those who used cocaine. As a class of drugs, amphetamines are sympathomimetic agents that produce stimulation of α- and β-adrenergic receptors. This results in elevated blood pressure and pulse. The user describes a sense of well-being, decreased fatigue, and enhanced sensory perception. Amphetamines are considered to have a high abuse potential.[14] Although effects of amphetamine use in pregnancy have not been widely investigated, the reported maternal and neonatal consequences of amphetamine use do not appear to be as dramatic as those of cocaine.[15-18]

β-Sympathomimetics, decongestants, and common over-the-counter anorexiants can yield positive toxicologic results for amphetamines. The historic data collection did not include recent use of the above medications, except for ephedrine use in association with regional anesthesia and β-sympathomimetics for tocolysis. The use of decongestants and anorexiants in a laboring woman is often not suspected, inquired about, or documented in the medical records. Further studies are needed to confirm our findings.

The EMIT reagents detect cocaine use within 24 to 72 hours of obtaining the specimen. Other studies have shown that a careful history is needed to elicit prior drug use.[19] The historical data from the patients' records were obtained by residents, nurses, and attending physicians working in a busy labor suite. It is likely that a thorough history of drug use was not taken. Therefore the actual rate of drug use in our population may be higher than reported in this study. Other methods of drug detection such as hair analysis may allow a more complete identification of substance use during pregnancy.[19]

In conclusion, we found a high prevalence of cocaine and amphetamines in urine toxicology screens in

women admitted to our labor suite. Drug use was rarely detected by routine medical history alone. The high prevalence of amphetamine use has not been reported by others and merits further study. Our data demonstrate that urine toxicology screening of all pregnant women is necessary if all women and infants at risk for the complications of drug abuse are to be identified and treated.

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A comparison of the effect of epidural, general, and no anesthesia on funic acid-base values by stage of labor and type of delivery

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The effect of epidural anesthesia on neonatal acid-base status, before, during, and after labor, was determined by review of funic blood-gas values from 142 women with normal term pregnancies and normal fetal heart rate patterns. Funic acid-base parameters were compared by type of anesthesia when stratified by mode of delivery (vaginal, cesarean section in the active phase of labor, or elective cesarean section). Use of epidural analgesia for vaginal delivery was associated with significantly longer labor, lower umbilical arterial pH, higher arterial P_{CO_2} and arterial bicarbonate values. In women who had cesarean section in the active phase of labor, use of epidural anesthesia was associated with significantly lower arterial and venous P_{O_2} values when compared with women who received general anesthesia. Patients who had elective cesarean section with epidural anesthesia had funic acid-base values similar to women who had general anesthesia. Epidural analgesia-anesthesia offers no clear advantage to the uncompromised term fetus. (AM J OBSTET GYNECOL 1990;163:802-7.)

Key words: Acid-base balance, umbilical cord, obstetric anesthesia

It is commonly believed that use of epidural anesthesia offers an advantage to the fetus over general anesthesia. Gale et al.[1] studied a group of women who had cesarean sections and found a greater incidence of acidemia, hypercarbia, and need for respiratory assistance in infants born under general anesthesia. Other investigators found that use of general anesthesia results in lower Apgar scores and increased need for neonatal resuscitation when compared with use of a regional anesthetic.[2, 3] Some authors document no difference in neonatal condition with respect to funic acid-base values, 1- and 5-minute Apgar scores, and time to sustained respiration between infants born by elective cesarean section under epidural anesthesia versus general anesthesia.[4]

Conversely, use of epidural anesthesia, despite its known safety, is associated with a reduction in maternal blood pressure,[5] which is the primary determinant of uterine blood flow. Medications given to combat hypotension may also impair uterine perfusion.[6]

The definition of normal values for acid-base parameters depends largely on the population under study.[7, 8] Umbilical arterial acid-base parameters reflect the impact of intrapartum events and specifically aid in the evaluation of the depressed newborn.[9, 10]

The effect of mode of anesthesia on immediate neonatal outcome as measured by umbilical cord acid-base balance has not been completely elucidated for both vaginally delivered and abdominally delivered patients. The purpose of this investigation was to determine the impact of type of anesthesia, by type of delivery, on a carefully selected group of uncompromised infants born to normal women after an uncomplicated term pregnancy. We analyzed funic acid-base status with or without epidural analgesia in the absence, midst, and conclusion of labor, that is, at elective cesarean section, at cesarean section performed in the active phase of labor, and at vaginal delivery, respectively.

Patients and procedures

Barnes Hospital patient charts from January 1986 through December 1987 were reviewed. The study population consisted of 142 women who were delivered of infants weighing 2500 to 3999 gm, at 36 to 41⅐ weeks' gestation, with normal fetal heart rate patterns and available umbilical arterial and venous acid-base values. No patients with induced labors were included. Patients with antenatal risk factors thought to impact on acid-base status were also excluded from study. All medical and obstetric complications of pregnancy that could potentially contribute to adverse neonatal out-

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6/6/22340

come were excluded (e.g., diabetes mellitus, hypertensive illnesses, antepartum hemorrhage, asthma, sickle cell disease, Rh isoimmunization, and congenital malformations). Criteria for exclusion on the basis of fetal heart rate patterns were as follows: late decelerations, severe variable decelerations (to 60 beats/min for 60 seconds), prolonged decreased short-term or long-term variability, baseline tachycardia of ≥160 beats/min, and prolonged bradycardia (>5 minutes) within 30 minutes of delivery. Those pregnancies complicated by thick meconium (>2+ on a scale from 0 to 4+) were also excluded.

These patients were stratified into six groups based on mode of anesthesia and type of delivery. Group 1 contained women with spontaneous vaginal deliveries without regional anesthesia. They may have received narcotic analgesia or local anesthesia for labor and delivery. Group 2 subjects had spontaneous vaginal deliveries with epidural analgesia. Group 3 patients had cesarean section during the active phase of labor with general anesthesia. Group 4 was composed of women who underwent cesarean section during the active phase of labor with epidural anesthesia. Subjects were excluded from groups 3 and 4 for cervical dilatation <4 cm and cesarean section before the onset of active labor, as defined by Friedman.[11] Groups 3 and 4 were nonelective, surgical deliveries primarily in women after an arrest of labor or because of malpresentation in active labor. The use of oxytocin constituted an exclusion criterion for all but groups 3 and 4, in whom it was used as needed for augmentation of labor. Women in group 5 had cesarean delivery before the active phase of labor with general anesthesia. Group 6 patients underwent cesarean section without active labor with epidural anesthesia. Groups 5 and 6 were largely composed of patients having elective or semielective cesarean sections.

Funic blood was collected from a doubly clamped segment of umbilical cord immediately after vaginal or cesarean delivery. The samples were iced and within 15 minutes of collection, pH, P_{O_2}, P_{CO_2}, and hemoglobin levels were directly measured with a Radiometer (Copenhagen) blood gas analyzer model ABL 2. Base excess (deficit) was calculated.

Anesthesia was conducted by an anesthesiologist or nurse anesthetist as follows. Those undergoing general anesthesia for cesarean section, while positioned in left lateral tilt position, had a rapid-sequence induction and were preoxygenated with 100% oxygen in all cases. Thiopental sodium, 3 to 5 mg/kg, and succinylcholine, 1.0 to 1.5 mg/kg, were used before intubation with cricoid cartilage pressure. Those undergoing epidural analgesia for labor received volume loading with 500 to 1000 ml of lactated Ringer's solution before placement of a catheter in the epidural space. A test dose of 2% lidocaine with epinephrine was given, followed by an analgesic dose of 0.125% to 0.25% bupivacaine hydrochloride with or without fentanyl, 50 to 100 μg, at the discretion of the anesthesiologist. Perineal anesthesia was accomplished with 1.5% lidocaine or 2% to 3% 2-chloroprocaine. Epidural anesthesia for cesarean section was performed under similar conditions; however, 0.5% bupivacaine hydrochloride or 3% 2-chloroprocaine was used at a dose appropriate for the patient's height to achieve a block at the level of T4-6. For cesarean section volume preload was 1500 to 2000 ml of normal saline solution. Intravenous ephedrine, in 5 mg increments, was used in all cases of hypotension refractory to hydration and change in maternal position.

Table I. Description of groups

Group	*Description*	*n*
1	Vaginal delivery without anesthesia	29
2	Vaginal delivery with epidural analgesia	25
3	Cesarean section in active labor with general anesthesia	16
4	Cesarean section in active labor with epidural anesthesia	24
5	Elective cesarean section with general anesthesia	21
6	Elective cesarean section with epidural anesthesia	27

The unpaired Student *t* test was used to compare means from the groups associated with epidural analgesia, anesthesia, or both, and those without. Nonparametric data were compared with Fisher's exact test. Duration of labor was logarithmically transformed to a normal distribution. Multiple analysis of variance, general linear models analysis of variance and covariance, and stepwise multiple regression were used for multiple comparisons.

Results

One hundred forty-two women were included in the study. The patients were divided into the six defined groups by mode of anesthetic and type of delivery (Table I). Demographic characteristics of the study population are presented in Table II. Demographic characteristics were similar among groups; however, the patients in group 2 were younger and of lower parity than those in group 1 ($p < 0.05$ and $p < 0.005$, respectively). Length of gestation and birthweight were similar among groups compared.

Table III demonstrates the indications for cesarean section by group. The category of "other" in group 3 included an infant with an asymptomatic funic presentation noted on ultrasonographic scan. Group 5 women included one patient who had a scheduled cesarean

Table II. Demographic data

Group	n	Age (yr)	Race (% white)	Parity
1	29	27.0 ± 5.4	7 (24%)	2.2 ± 2.1
2	25	23.1 ± 6.2	11 (44%)	0.8 ± 0.75
3	16	26.0 ± 4.6	7 (44%)	1.1 ± 1.27
4	24	24.3 ± 5.5	9 (38%)	0.3 ± 0.69
5	21	26.8 ± 4.2	8 (38%)	1.2 ± 0.85
6	27	27.2 ± 6.4	11 (39%)	1.7 ± 0.87

Table III. Indications for cesarean section

	Group							
	3		4		5		6	
Indication	No.	%	No.	%	No.	%	No.	%
Repeat	3	19	0	0	15	71	24	89
Malpresentation	6	37	0	0	1	5	1	4
FTP-CPD	4	25	23	96	0	0	0	0
HSV	2	13	1	4	0	0	2	7
Other	1	6	0	0	5	24	0	0
TOTAL	16	100	24	100	21	100	27	100

FTP-CPD, Failure to progress–cephalopelvic disproportion; *HSV,* active herpesvirus infection.

hysterectomy, one with idiopathic thrombocytopenic purpura, one with a scheduled cholecystectomy, and two with maternal intracranial arteriovenous malformations. The decision with regard to the form of anesthesia was largely determined by indication for cesarean section and by the presence or absence of an indwelling epidural catheter. Acidosis, defined as umbilical arterial pH ≤ 7.15,[12] was not observed in any group.

Funic arterial and venous acid-base results are presented in Table IV. Fig. 1 graphically demonstrates the arterial pH data for the six groups. There were statistically significant differences in arterial pH, P_{CO_2}, and bicarbonate between groups 1 and 2. There also were significantly lower values of arterial and venous P_{O_2} in the newborns from the group 4 compared with group 3. No significant differences between funic acid-based values were evident between groups 5 and 6.

There were no infants with Apgar scores <7 at 5 minutes in any of the groups studied. There were seven infants with Apgar scores <7 at 1 minute: one (3.4%) in group 1, one (4.0%) in group 2, two (8.3%) in group 4, and three (14.3%) in group 5. These differences were not statistically significant, even for group 5 versus group 6 ($p = 0.077$, Fisher's exact test).

Hypotension necessitating administration of ephedrine occurred in each of the three epidural analgesia/anesthesia groups. Ephedrine was required in 5 of 25 patients (20%) in group 2, 7 of 24 cases (29%) in group 4, and 14 of 27 (52%) in group 6. This finding is not surprising when the increased dosage of epidural agent required to achieve surgical anesthesia over labor analgesia is considered. The occurrence of hypotension did not affect the overall results of the eight outcome measures (Wilkes' lambda [10, 66.5] = 0.8917, $p = 0.540$) or any of the individual outcome measures ($p > 0.2$).

Women treated with epidural analgesia had longer labors. The patients in group 1 had a mean stage I duration of 7.78 ± 5.23 hours and mean stage II duration of 0.33 ± 0.29 hours. The mean length of labor in group 2 was 13.09 ± 7.94 hours, and 0.87 ± 0.50 hours for stages I and II, respectively. Among vaginally delivered infants the highly significant difference in active-phase labor duration between epidural compared with no anesthesia ($F = 9.64$, $p < 0.01$) was not explained by parity ($F = 0.00$, $p = 1.00$). There was an increased duration of the second stage with nulliparity ($F = 12.98$, $p < 0.001$) and with use of epidural anesthesia ($F = 16.53$, $p < 0.001$), which were independent of each other ($F = 1.45$, $p = 0.23$).

For the women who were delivered vaginally in groups 1 and 2, multiple statistical analyses were made of significant acid-base differences to control for parity, duration of active labor, duration of second stage, and to determine a source of the observed differences. Funic arterial pH was significantly higher in parous than in nonparous patients. The effect of anesthesia on pH was significant even when controlled for parity ($p < 0.05$). There was a fall in pH observed with increased duration of the second stage of labor ($p < 0.05$). The effects on pH of nulliparity and epidural anesthesia were dependent on longer duration of the second stage of labor. Active-phase duration of labor demonstrated no effect on pH. Similarly, the decrease in funic venous P_{O_2} in the epidural group was dependent on length of second-stage labor. The observed increased arterial P_{CO_2} and bicarbonate levels in group 2 were not dependent on duration of labor, duration of the second stage of labor, or parity. None of these variables were independently associated with bicarbonate or P_{CO_2}.

Comment

Controversy exists with regard to the effects of epidural anesthesia on the course of labor and the metabolic status of the newborn infant despite its widely accepted use. Some studies have shown a tendency toward mild fetal metabolic acidemia in labors with epidural analgesia to be less than that found in unanesthetized pregnancies,[13, 14] whereas others have found no differences.[15] Problems in interpreting the literature relate to the lack of standardization of methodology

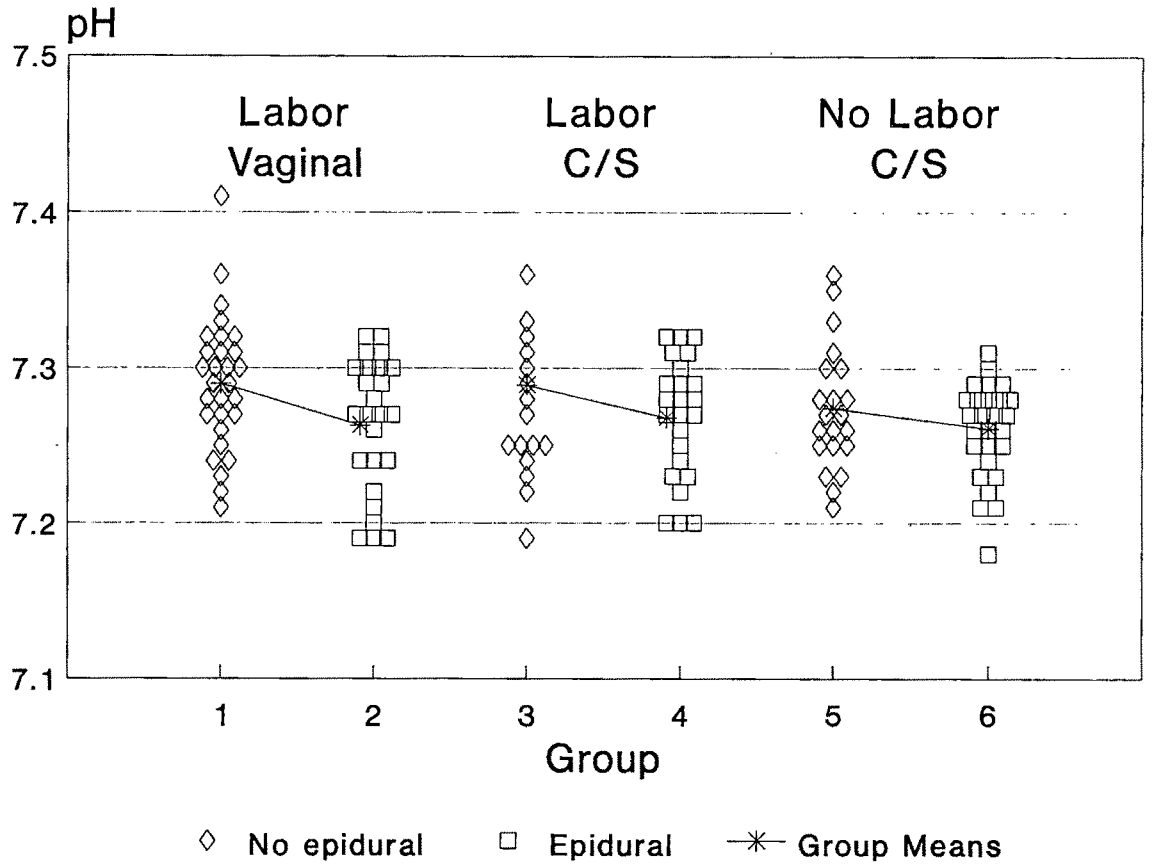


Fig. 1. Mean umbilical arterial pH values and distribution presented by group. A statistically significant difference was noted between groups 1 and 2 ($p < 0.05$, Student t test).

and patient characteristics, and technical improvements over time.

Gale et al.,[1] who studied a group of women who had elective and nonelective cesarean sections, found that epidural anesthesia offers neonatal advantages because the requirement for neonatal respiratory assistance was higher among women who received general anesthesia. However, mothers with high-risk complications were included in groups undergoing nonelective cesarean section, possibly confounding their results. They found no difference in mean acid-base values between the epidural and general anesthesia groups among those delivered electively, in accordance with our study. Their data indicated an increased need for neonatal respiratory assistance after general anesthesia for elective cesarean section. These results were not duplicated by our study, nor were they explained by their acid-base values, possibly indicating a direct effect of general anesthetic agents on newborn respiratory efforts. Ong et al.[2] demonstrated lower 1-minute Apgar scores in infants delivered by cesarean section with general anesthesia under elective conditions, and lower 1- and 5-minute scores, and greater requirements for intubation and artificial ventilation, in those delivered under general anesthesia in urgent conditions, compared with those delivered under similar conditions with regional anesthesia. Anesthetic technique did not affect perinatal survival.[2] Conversely, Fox et al.[4] found no difference in neonatal Apgar scores, funic acid-base values, or increased time to sustained respiration after elective cesarean section between infants delivered with epidural compared with general anesthesia, in accordance with our findings.

The mild reduction in funic acid-base values associated with epidural analgesia in the infants delivered vaginally was partially associated with an increased length of labor in the regional anesthesia group. Katz et al.[16] demonstrated a significant rise in lactate and decrease in pH in the umbilical artery, with increasing lengths of stage II labor over 15 minutes in women who had no anesthesia. These results have been confirmed by others.[17] Thorp et al.[18] demonstrated an increased length of labor and rate of cesarean section for dystocia in nulliparous women delivered with use of an epidural anesthetic.[18] We found a highly significant increase in the length of stage II labor in the group delivered vaginally who had epidural analgesia, which was independent of parity, and significance held for both nullipa-

Table IV. Umbilical cord acid-base values

	Vaginal birth			*Cesarean section—Active phase*		
	Group one (n = 29; no epidural)	*Group two (n = 25; epidural)*	*p value*	*Group three (n = 16; general)*	*Group four (n = 24; epidural)*	*p value*
Arterial						
pH	7.29 ± 0.04	7.26 ± 0.04	$p < 0.05$	7.27 ± 0.04	7.27 ± 0.04	NS
P_{CO_2}	48.1 ± 6.25	54.5 ± 6.56	$p < 0.001$	53.5 ± 7.97	52.1 ± 7.13	NS
P_{O_2}	19.9 ± 5.00	18.0 ± 5.36	NS	20.7 ± 6.55	16.9 ± 4.76	$p < 0.05$
Bicarbonate	23.2 ± 2.82	25.5 ± 1.87	$p < 0.002$	25.4 ± 2.78	24.5 ± 2.43	NS
Base excess	−4.8 ± 2.6	−3.9 ± 1.8	NS	−3.7 ± 2.2	−4.4 ± 1.9	NS
Venous						
pH	7.37 ± 0.05	7.35 ± 0.04	NS	7.33 ± 0.04	7.33 ± 0.05	NS
P_{CO_2}	39.4 ± 5.46	41.9 ± 5.98	NS	45.5 ± 6.11	44.3 ± 7.27	NS
P_{O_2}	31.0 ± 7.69	27.7 ± 6.95	$p = 0.05$	36.3 ± 7.45	28.0 ± 10.3	$p < 0.01$
Bicarbonate	23.1 ± 1.93	24.4 ± 1.67	NS	24.3 ± 2.10	23.8 ± 2.37	NS
Base excess	−2.8 ± 2.0	−2.2 ± 1.5	NS	−3.0 ± 1.7	−3.3 ± 2.1	NS

rous and parous gravid women. Length of labor fully explained the lower pH in this group.

Another reason for relative hypoxemia and hypercarbia associated with the use of epidural analgesia is hypotension as a result of sympathetic blockade. Brizgys et al.[19] demonstrated a significant decrease in mean funic arterial pH values in women who experienced hypotension at cesarean section; however, the magnitude of this difference never exceeded 0.04 pH units. In our series transient symptomatic hypotension, as evidenced by the need for ephedrine, did not contribute to any funic acid-base changes. In no instance was maternal hypotension prolonged.

The indication for cesarean section and presence or absence of an epidural catheter at the time of the decision influenced the choice of anesthesia. Patients with arrested labor from cephalopelvic disproportion were more inclined to have regional rather than general anesthesia for cesarean section (96% vs 25%), whereas those undergoing cesarean section in the active phase of labor because of malpresentation of the fetus were more likely to have general anesthesia (37% vs 0%). The belief that use of epidural rather than general anesthesia is advantageous to the fetus contributed to the preponderance of epidural analgesia for elective repeat cesarean section in our institution.

In summary, analysis of funic acid-base determinations at birth demonstrates that use of epidural anesthesia offers no clear-cut advantage to the respiratory and metabolic status of the normal, term fetus. In fact, there were higher arterial P_{CO_2}, lower pH, and higher arterial bicarbonate values in patients with normal labor who were delivered vaginally with epidural anesthesia than in those without. The pH findings were explained by longer labors associated with epidural analgesia and were independent of parity. In women undergoing cesarean section in the active phase of labor, use of epidural anesthesia was associated with significantly lower arterial and venous P_{O_2} values compared with general anesthesia. These differences appear to be independent of length of labor or incidence of symptomatic hypotension. When the previously published normal ranges for funic acid-base values are considered, it is unlikely that these differences are clinically important for the term fetus with a normal electronic monitor pattern. For patients who had cesarean sections electively or before the active phase of labor, use of epidural anesthesia did not result in improved funic blood gas values when compared with general anesthesia.

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Cesarean section—Not active		
Group five (n = 21; general)	*Group six (n = 27; epidural)*	*p value*
7.27 ± 0.04	7.26 ± 0.03	NS
53.1 ± 7.35	54.5 ± 6.54	NS
19.5 ± 5.98	17.5 ± 5.09	NS
25.3 ± 2.91	25.2 ± 2.07	NS
−2.9 ± 2.8	−4.1 ± 1.7	NS
7.34 ± 0.04	7.34 ± 0.03	NS
46.1 ± 6.74	43.9 ± 3.81	NS
32.7 ± 9.14	35.3 ± 9.11	NS
24.7 ± 2.43	24.2 ± 1.30	NS
−2.0 ± 1.5	−2.8 ± 1.3	NS

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Effect of uterine contractility and maternal hypotension on prolonged decelerations after bupivacaine epidural anesthesia

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Patients with prolonged decelerations after bupivacaine epidural anesthesia were matched with control patients. It was found that there were no differences in the decrease in mean arterial blood pressure after epidural anesthesia between those with prolonged decelerations (5 ± 9 mm Hg) and those without (5 ± 9 mm Hg). Uterine hypertonus was suggested as a cause in the prolonged deceleration group as a result of a higher rate of subjective impressions of uterine hypertonus (82% vs 11%) and more frequent use of terbutaline (30% vs 0%) after epidural anesthesia. With patients with internal uterine pressure monitors used as their own controls, it was also found that basal uterine tone was higher during periods when the deceleration occurred (26 ± 9 mm Hg) than when it did not (13 ± 4 mm Hg), and in comparison to windows before epidural anesthesia (12 ± 5 mm Hg). (AM J OBSTET GYNECOL 1990;163:808-12.)

Key words: Bupivacaine, epidural anesthesia, prolonged deceleration, maternal hypotension, uterine hypertonus

A prolonged fetal heart rate (FHR) deceleration after the administration of epidural anesthesia is an anxiety-producing event that may follow this common form of analgesia. This event has not generated the degree of investigation that occurred with FHR decelerations after paracervical blocks for pain relief in labor. The frequency of prolonged decelerations after bupivacaine epidural anesthesia has been reported by Vroman et al.,[1] and Abboud et al.[2, 3] as between 7.9% and 12.5%. Abnormal FHR patterns have been noted to be more common with use of bupivacaine than chloroprocaine or lidocaine.[3] The incidence of prolonged decelerations after paracervical blocks with bupivacaine is higher (23%[4]) and is contraindicated for this technique.[5] The exact mechanism responsible for these potentially serious changes in FHR has not been clearly delineated. In this study the association of prolonged decelerations after intrapartum bupivacaine epidural anesthesia with changes in uterine activity and the lack of an association with changes in maternal blood pressure is reported.

Material and methods

This retrospective, case-controlled study was conducted at Long Beach Memorial Women's Hospital, an obstetric tertiary care center in southern Los Angeles County.

Patients with prolonged decelerations constituted the study group. Between July 1, 1988, and July 1, 1989, patients were identified by nursing staff and physicians, and their names were forwarded to the first author. For the year 1987, a computerized search was made of the hospital data base of obstetric patients, cross-referencing the diagnosis of fetal bradycardia with epidural anesthesia. Eligibility criteria included a prolonged deceleration with a decrease of the FHR below 120 beats/min for at least 2 minutes' duration within 1 hour of the completion of the initial loading dose of 0.25% bupivacaine epidural anesthesia. Twenty-seven patients were selected for study. Twelve had internal uterine pressure catheters. Subjects were rejected primarily for poor-quality FHR tracings or the use of anesthetic agents other than bupivacaine.

The interpretation of hypertonus as abnormal basal uterine tone was subjective; however, the following guidelines were used. An elevation of basal uterine tone of ≥10 mm Hg between contractions on two or more consecutive intervals, compared with prior intervals, was considered to have clinical significance. This degree of change was also used for patients with external monitors even though it is acknowledged that this amount of change is only relative and not absolute.

Each patient of the study group was matched by age (±3 years), parity, and gestational age (±4 days) with two control patients who had bupivacaine epidural anesthesia during labor without prolonged decelerations. The control subjects were selected randomly from the delivery logbooks of 1987 and 1988. Patients who had epidural anesthesia for cesarean section only were excluded from the control group. Each of the twelve patients in the study group with internal uterine pressure catheters was matched with at least one control patient who also had an internal uterine pressure catheter

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before and after the administration of epidural anesthesia.

Bupivacaine 0.25% was the most commonly selected epidural agent and was used in all study and control group patients. Prehydration with 500 to 1500 ml of isotonic fluids was given in all procedures. Epidural catheters were placed with the women in the sitting position in all but three patients in the study and control groups. The three patients who had catheters placed while on their sides were in the study group with prolonged decelerations. Epidural anesthetics were given as an initial dose of 9 to 14 ml (12.4 ± 0.9 ml) of 0.25% bupivacaine. In all cases a test dose of 2 to 4 ml was given before the remainder of the initial dose. Epinephrine was not used in any of the anesthetic solutions. In three cases patients who had not received adequate relief by 20 minutes received another injection of 5 ml. In the study group this occurred with one patient at 23 minutes and was immediately followed by a prolonged FHR deceleration at 24 minutes. Two patients in the control group received a similar dose at about the same time. One was followed by a solitary late deceleration. The total time required to place the epidural catheter and administer the initial dose of bupivacaine was usually <15 minutes. Administration of the anesthetic agent from test dose to final dose usually required 5 minutes. After the initial dose of bupivacaine was given the patient was placed on her side and given a continuous infusion of 4 to 7 ml/hr (5.9 ± 0.9 ml) of 0.25% bupivacaine. The patient was then moved from one side to the other to ensure a uniform block. Blood pressure recordings were taken by the nursing staff with a sphygmomanometer with the patient either on her side or supine with a wedge. Blood pressure was converted to mean arterial pressure, calculated as the diastolic pressure plus one third of the difference of systolic and diastolic pressure. Recordings were made before the procedure and at 5-minute intervals after epidural anesthesia for 25 minutes, then at 15 minutes, and then at 30-minute intervals.

Data for this study were obtained from maternal charts and FHR strips. The study focused on uterine activity, FHR, and blood pressure during the hour before and after administration of the epidural anesthesia. The time of epidural anesthesia was determined as the last injection of the initial dose of bupivacaine as noted on the FHR monitor strip. This 2-hour period of the FHR strip was divided into 10-minute windows, 6 minutes before and 6 minutes after the initial dose. Data on FHR, deceleration patterns, uterine activity, medications, blood pressure, and cervical change were recorded for each 10-minute window. Patients with internal uterine pressure catheters had uterine activity recorded as Montevideo units (peak contraction pressure minus the average basal tone before and after the contraction) and basal uterine tone (the nadir of uterine pressure between contractions averaged for the window). Only the number of contractions per 10 minutes was recorded for patients with external monitors. Patients who had epidural anesthesia for cesarean section only were not specifically excluded but none were detected with prolonged decelerations after anesthesia administration. This may be because they were monitored for only a short time after catheter placement.

Statistical tests included χ^2, Fisher's exact test, paired t test, and Wilcoxon ranked-sum test, as appropriate for the given instance. Calculations of Fisher's exact test and Wilcoxon ranked-sum test were done with the BMDP Program (Program 3D/3S, 1988, Westwood, Calif.). Data were considered statistically significant at the $p < 0.05$ level. All tests were two-sided. All variances expressed in this article are expressed as 1 SD.

Results

The frequency of prolonged decelerations after bupivacaine epidural anesthesia was estimated at 8.5%, based on the random sampling of patients selected for control subjects. This estimate is conservative as patients with this phenomenon had already been removed from the sample as described previously. There were five patients who were rejected as control subjects because of the presence of a prolonged deceleration after epidural administration.

The similarities in the two groups of patients are summarized in Table I. There were no significant differences in birthweights, number of cesarean sections, or use of oxytocin. High-risk factors were rare in both groups. There were two patients with hypertensive disorders in the control group and one in the deceleration group. Overall uterine activity, measured by Montevideo units, was higher in the deceleration group (Table II). When only uterine activity before epidural anesthesia was compared this difference lost its statistical significance. The control group labored longer after epidural administration than the study group. There were no differences between the two groups in initial anesthetic doses or in the rate of the continuous infusion. None of the patients with prolonged decelerations or in the control group experienced seizures or signs of intravenous injection after the administration of the epidural anesthetic. Patients were nulliparous 70% of the time in both groups.

The prolonged decelerations occurred at an average of 13.3 ± 9.6 minutes from the end of the initial dose of epidural anesthetic and lasted an average of 6.6 ± 2.9 minutes. The average decrease in FHR was 64 ± 15 beats/min from a baseline of 129 ± 9 beats/min.

Blood pressure. Blood pressure measurements were taken during the prolonged deceleration in 63% of the study group and averaged 77 ± 7 mm Hg. The average mean arterial pressure during the deceleration did not

Table I. Characteristics of patients with prolonged decelerations after epidural anesthesia and those assigned to the control group

	Study group (n = 27)	*Control group (n = 54)*
Maternal age (yr)	28.9 ± 4.7	28.3 ± 4.6
Gestational age (wk)	39.9 ± 1.5	40.1 ± 1.5
Birth weight (gm)	3459 ± 475	3549 ± 476
Apgar scores		
1 min	7.7 ± 1.7	8.4 ± 0.7
5 min*	8.8 ± 0.6	9.0 ± 0.2
No. < 7 at 1 min	3 (11%)	1 (2%)
No. < 7 at 5 min	1 (4%)	0
Epidural		
Initial dose†	12.4 ± 0.9	12.5 ± 0.8
Continuous infusion‡	5.9 ± 0.8	5.9 ± 1.0
Oxytocin use	10 (37%)	24 (44%)
Vaginal delivery	17 (63%)	42 (78%)
Meconium	6 (22%)	7 (13%)
Time from epidural to delivery (min)§	196 ± 196	303 ± 177

Numbers with variances are averages. Variances indicated are standard deviations.

*Statistically significant, $p < 0.05$, Wilcoxon ranked-sum test.

†Milliliters bupivacaine 0.25%.

‡Milliliters per hour of bupivacaine 0.25%.

§Statistically significant, $p < 0.05$, paired t test.

Table II. Average uterine activity in patients with and without prolonged decelerations after epidural anesthetic and monitoring with internal uterine pressure catheters

	Study group (n = 12)	*Control group (n = 12)*
All windows		
Basal tone (mm Hg)	16 ± 4	17 ± 5
Montevideo units*	176 ± 53	136 ± 45
Before epidural		
Basal tone (mm Hg)	12 ± 5	16 ± 5
Montevideo units	180 ± 60	146 ± 47

Numbers with variances are averages. Variances indicated are standard deviations.

*Statistically significant, $p < 0.05$, paired t test.

differ significantly from the average mean arterial pressure in the hour after epidural anesthesia (77 ± 8 mm Hg). The statistical comparison of these two groups is sufficiently powerful to have an 80% probability of detecting a difference of 7 mm Hg. Blood pressure comparison between patients with prolonged decelerations and controls are summarized in Table III. Mean arterial pressure changed an average of 5 mm Hg with epidural anesthesia in both the patients with prolonged decelerations and the control patients without these decelerations. However, there was no significant difference beteen the two groups. The data were sufficiently powerful to have an 80% probability of detecting a difference of 13 mm Hg. There was also no significant difference between the two groups in the number of patients who had a 10% to 20% decrease in blood pressure measurements. There were no patients in either group with ≥30% decrease in mean arterial pressure. Ephedrine was used only once in the control group and never in the study group.

Uterine activity. Patients with prolonged decelerations after epidural anesthesia were significantly more likely to have a subjective impression of uterine hypertonus (14/17 vs 6/54, $p < 0.05$, χ^2). There were 10 patients with external tocometry in the deceleration group who were not included in these numbers because of an absence of recorded contractions at the time of the prolonged deceleration. A significant difference was found in the women who received terbutaline (8/27 vs 0/54, $p < 0.05$, Fisher's exact test) after epidural anesthesia. Patients with prolonged decelerations and an internal uterine pressure catheter were also more likely to have received terbutaline than those with prolonged decelerations and external monitors (6/12 vs 2/15), but this did not achieve statistical significance.

Attempts to quantitatively identify patients with increased uterine activity or hypertonus were surprisingly difficult. Data from external tocometry were generally not helpful. Analysis of data from internal uterine pressure catheters was more helpful. With the patient serving as her own control, it was noted that basal uterine tone was significantly more elevated in windows when the prolonged deceleration took place compared with the other windows in which there was no prolonged deceleration (26 ± 9 vs 13 ± 4 mm Hg; $p < 0.05$, paired t test). This was also true if the windows preceding administration of epidural anesthesia were used for comparison (26 ± 9 vs 12 ± 5 mm Hg; $p < 0.05$, paired t test). Similar analyses of Montevideo units also showed an increase, but this did not achieve statistical significance. Uterine pressure during hypertonic contractions can exceed the scale on the FHR tracing, thus making this analysis difficult (Fig. 1).

There were statistically significant differences in the average 5-minute Apgar scores. These differences were so small however, that it is doubtful that they are of clinical significance. The difference in Apgar scores <7 at 1 and 5 minutes was not significant. Among the four infants with Apgar scores <7 at 1 minute, all were delivered at least 1 hour after administration of epidural anesthesia or prolonged deceleration. Conversely, none of the nine infants born within 1 hour of administration of epidural anesthesia or the end of the prolonged deceleration had an Apgar score <7 and only two had scores of 7.

Comment

The cause of prolonged decelerations after administration of epidural anesthesia has not been clearly established. Cibils[6] and Gibbs and Noel[7] demonstrated the ability of anesthetic agents to cause uterine artery

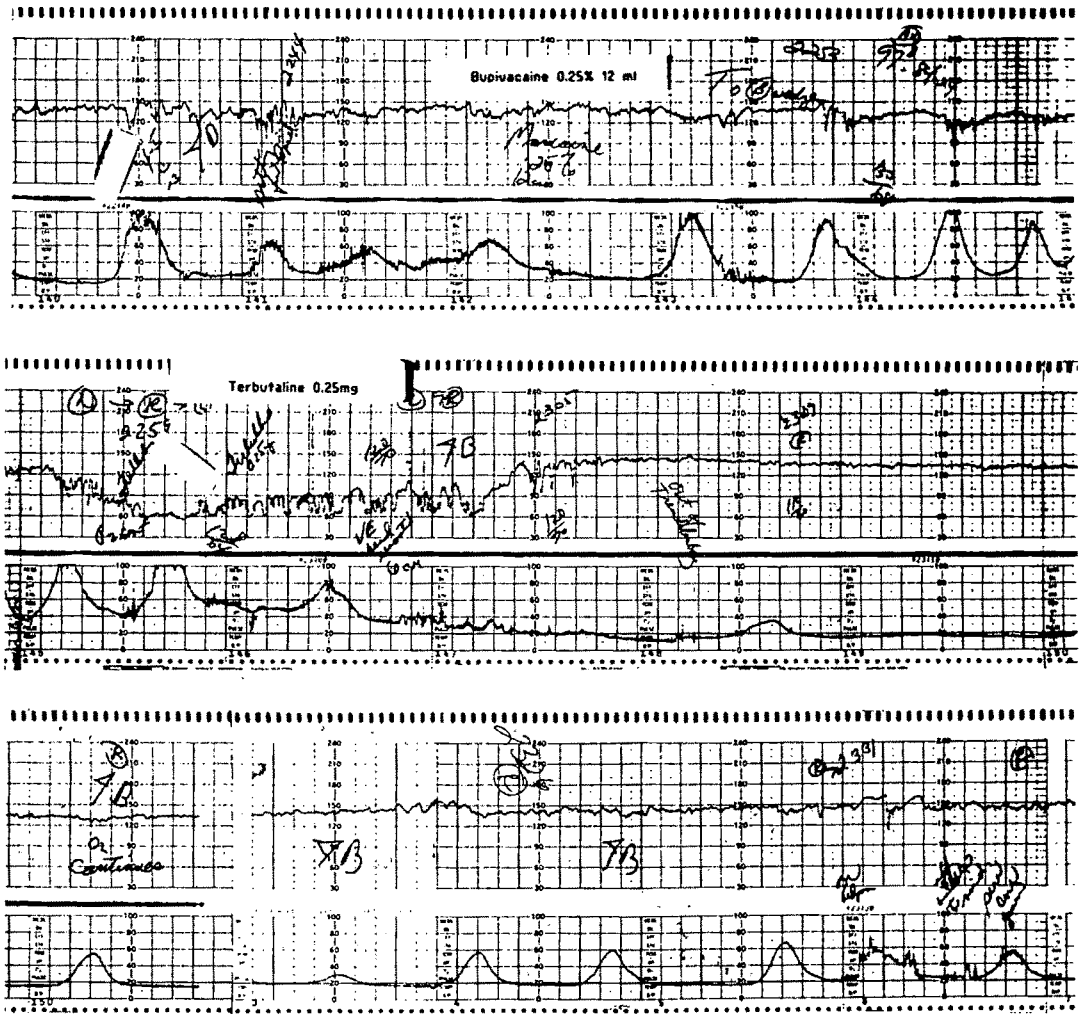


Fig. 1. A representative example of a patient with an internal uterine pressure catheter and a prolonged fetal heart rate deceleration after bupivacaine epidural anesthesia.

constriction in vitro. Fishburne et al.,[8] in their work with chronic preparations of fetal lambs, found that anesthetic agents that include bupivacaine stimulate vasoconstriction of uterine and placental vessels. They also found an increased uterine contractility and tone which, in turn, decreased uteroplacental blood flow. This decrease in uterine blood flow would precede the uterine contractions; they concluded that the uterine artery vasoconstriction was independent of uterine contractility.

The question of decreased uterine blood flow occurring after bupivacaine epidural anesthesia has been addressed in vivo in human Doppler flow studies.[9, 10] These studies show no change or improvement in the systolic/diastolic ratios, but none of the studies included a fetus with a FHR deceleration. Furthermore, all patients in the two studies underwent elective repeat cesarean section and none were in labor.

Vroman et al.,[1] in their series of 126 patients who had induction of labor with amniotomy and oxytocin, found that uterine hypertonus was associated with prolonged decelerations in seven of 10 patients with this problem after bupivacaine epidural anesthesia.

Schifrin[11] found that the risk of pathologic FHR patterns and hypertonus after lidocaine epidural anesthe-

Table III. Mean arterial pressure in patients with prolonged decelerations after epidural anesthesia and in control group

	Study group (n = 27)	*Control group (n = 54)*
Mean arterial pressure (mm Hg)		
Before epidural	82 ± 8	81 ± 9
After epidural	77 ± 8	77 ± 9
Change	5 ± 9	5 ± 9
Mean arterial pressure drop (mm Hg)		
10%	8 (30%)	17 (31%)
20%	3 (11%)	5 (9%)
30%	0	0

Variances indicated are standard deviations. No statistically significant differences were observed.

sia was increased by the concomitant use of oxytocin. This observation could not be reproduced in our study. There was no difference in the frequency of oxytocin use in the prolonged deceleration group compared with control subjects.

The results of our study suggest that uterine hypertonus is, in fact, correlated significantly with the presence of prolonged FHR decelerations after bupivacaine epidural anesthesia. Blood pressure changes were not associated with patients with prolonged decelerations. The observed changes in mean arterial pressure in the deceleration group were actually quite similar to those in the control group. It is recommended that in the treatment of the fetus with a prolonged deceleration after epidural anesthesia that strong consideration be given to the use of a rapid-acting tocolytic agent such as terbutaline, particularly in patients with external monitors, in whom an accurate assessment of uterine activity can be nearly impossible. The presence of prolonged decelerations after bupivacaine epidural anesthesia appears to have minimal, if any, effect on immediate fetal outcome.

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The effect of amnioinfusion on uterine pressure and activity: A preliminary report

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Transcervical intrapartum amnioinfusion of normal saline solution is being used in a number of centers. Over the past few years indications for the procedure have included prophylaxis and treatment of intrapartum decelerations in both term and preterm gestations, dilution and lavage of meconium-stained amniotic fluid, and for direct administration of antibiotics within the amniotic cavity in cases of chorioamnionitis. Little is reported about the real or potential risks of this procedure to both the mother and fetus. Over the past 2 years we observed several isolated cases of increased uterine activity by palpation coupled with fetal distress during amnioinfusion. These instances prompted us to study in a systematic fashion the relationships between uterine tone and activity during intrapartum amnioinfusion. We measured uterine tone and quantitated uterine activity in 10 patients undergoing intrapartum amnioinfusion and compared values 20 minutes before, during, and 20 minutes after amnioinfusion. A significant increase in uterine tone ($p < 0.05$) was noted during and after the infusion. No difference in uterine activity was observed in any of the study periods. A case of uterine hypertonus and fetal bradycardia and a suggested procedure scheme for intrapartum amnioinfusion are presented. (AM J OBSTET GYNECOL 1990;163:813-8.)

Key words: Amnioinfusion, uterine tone, uterine activity

Amnioinfusion has been used with increasing frequency during the intrapartum period over the past few years. The technique has been primarily used to decrease or relieve variable decelerations during labor.[1-3] Additional studies have addressed the use of this technique in preterm premature rupture of membranes,[4] meconium-stained amniotic fluid,[5, 6] and intrauterine infection therapy with direct antibiotic instillation.[7]

In the first prospective randomized clinical trial with amnioinfusion Miyazaki et al.[2] described a significant decrease in variable decelerations in the amnioinfused group (51%) versus the noninfused group (4.2%). This was most significant in the nulliparous patients with relief noted in 66.7% of the amnioinfusion group versus 0% in the noninfusion group. There was also a significant decrease in the rate of cesarean section in these patients for fetal distress, 14.8% in the infusion group versus 47.8% in the noninfusion group.

In a randomized trial of amnioinfusion versus controls in preterm premature rupture of the membranes, Nageotte et al.[4] showed both a statistically significant difference in the incidence of all variable decelerations during the first stage of labor (2.4% versus 7.9%) and a significant decrease in severe variable decelerations during the second stage of labor in the amnioinfusion group as compared with controls (2.9% versus 10.1%). They also showed a significant difference in pH values between the treated and control groups.

A recent publication by Wenstrom et al.[5] described a successful decrease in the incidence of low 1-minute Apgar scores, meconium noted below the cords, and of operative deliveries with saline solution amnioinfusion in the presence of meconium-stained amniotic fluid. Similarly, Sadovosky et al.[6] reported an incidence of thick meconium noted at delivery of 5% in amnioinfused patients versus 62% of controls. In patients who had intrapartum amnioinfusion their fetuses also had a decreased incidence of acidosis (16% versus 38%) and meconium noted below the cords (29% versus 0%) as compared with controls.

Although the procedure of amnioinfusion with normal saline solution is generally believed safe, potential complications must be considered. Gimbel[8] posed the question of an increased incidence of umbilical cord prolapse after amnioinfusion; however, no substantiative reports have emerged.

An additional consideration relates to the potential occurrence of uterine hypertonus as a result of stretching of the myometrial muscle fibrils, which in turn causes increased passive tension. This theoretical effect coupled with clinical observations that suggest increased uterine tonus is most pertinent given a potentially compromised fetus or a patient with a prior uterine scar. Miyazaki[2] noted an "artificial increase" in the

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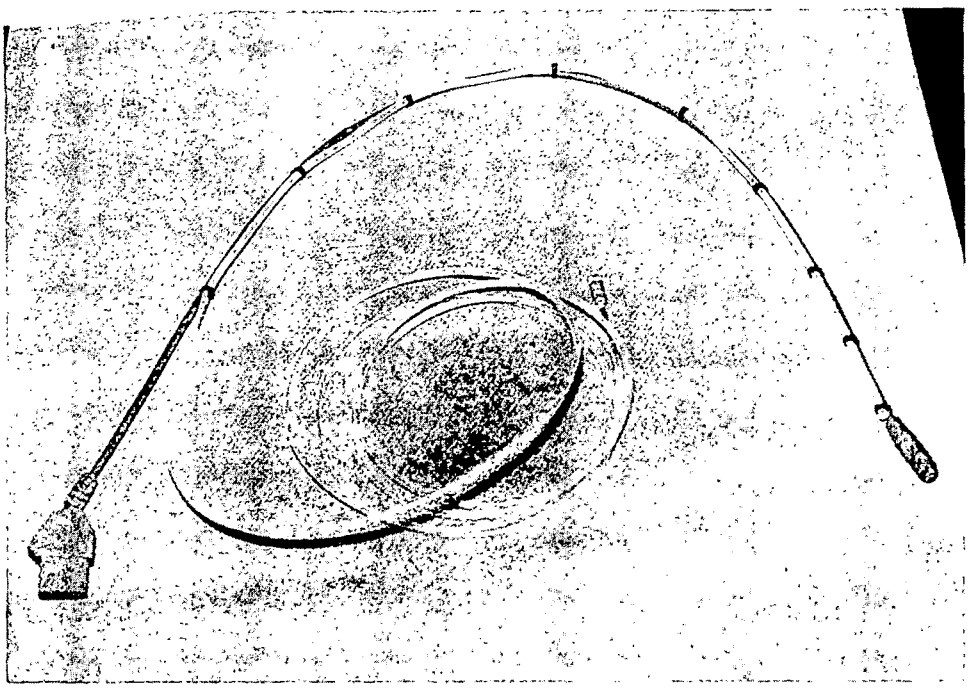


Fig. 1. Study device consisted of conventional fluid-filled intrauterine pressure catheter attached with heat-shrinkable tape to commercially available pressure-tipped intrauterine sensing device (Laurel Medical, Northfield, Minnesota).

resting tone of the uterus and attributes this "artificial increase" to resistance to outflow of the infusate through the holes of the catheter. Evaluation of the technique and existent data preclude a clear answer with regard to uterine tone.

The purpose of this study was to evaluate the effects, if any, on the uterine tone and activity associated with intrapartum transcervical amnioinfusion.

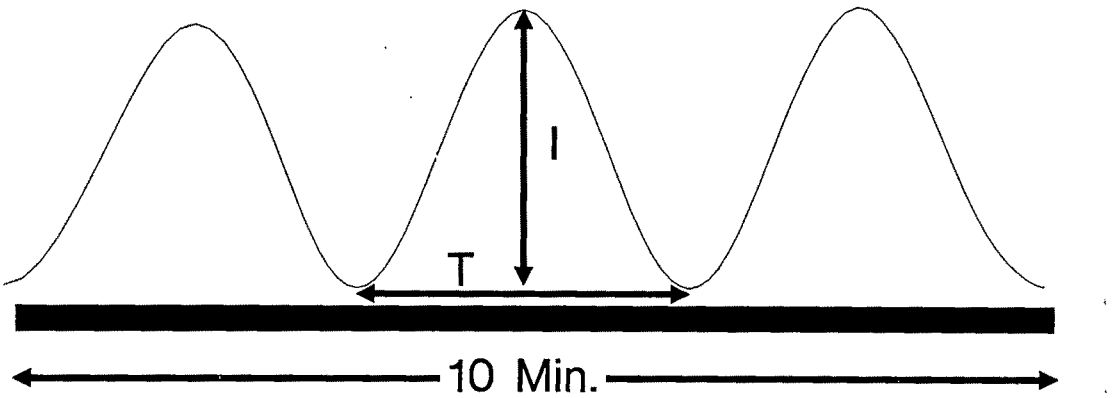
Material and methods

Patients were selected for amnioinfusion on the basis of any one or combination of the following criteria. Decreased amniotic fluid volume on the basis of amniotic fluid index of <5.0 cm, the presence of moderate to severe variable decelerations refractory to position changes, or the presence of meconium-stained amniotic fluid. Ten intrapartum patients with ruptured membranes, undergoing continuous direct fetal heart rate (FHR) monitoring, and deemed suitable for the insertion of an intrauterine pressure catheter were studied.

All patients had amniotic fluid volume assessed by the four-quadrant technique described by Rutherford et al.,[9] both before and immediately after the amnioinfusion. The infusion-study device consisted of a standard intrauterine pressure catheter attached with heat-shrinkable tape to a pressure-tipped sensor transducer, both of which are commercially available (Fig. 1). Normal saline solution, 250 ml warmed to 37° C was infused through the intrauterine pressure catheter by gravity flow.

The patient was prepared and draped for vaginal examination and the pressure-tipped device was zeroed to atmospheric pressure before insertion. After insertion of the study device the resting tone of the uterus was measured. The basal tone of the uterus as measured by the fluid-filled catheter was matched to that of the pressure-tipped catheter. For a period of 20 minutes before the infusion, the uterine activity from both systems was recorded on both a paper strip chart and on a multichannel tape recorder. After the 20-minute observation period the intrauterine pressure catheter was disconnected and the infusion of 250 ml warmed normal saline solution was begun. During the amnioinfusion, uterine tone and activity was continuously monitored with the pressure-tipped sensing device. After the infusion, the intrauterine pressure catheter was reconnected and the uterine activity was recorded for 20 minutes.

The uterine tone was measured in millimeters of mercury (mm Hg) and overall uterine activity was measured and expressed in Alexandria units[10] for the three study periods. Alexandria units are the average intensity of contractions, multiplied by the frequency of con-



Average I X Frequency / 10 min. X Average Duration (min.)

Fig. 2. Alexandria units are a qualitative unit of measurement of uterine activity. Alexandria unit = Average intensity *(I)* × Contraction frequency per 10 minutes × Average duration (in minutes) of contractions.

tractions in a 10-minute period, multiplied by the average duration of the contractions (Fig. 2).

Analysis of variance with subsequent Tukey-A and Tukey-B post hoc comparison was used for evaluation of both the uterine tone and uterine activity expressed in Alexandria units for the 20-minute preinfusion, during the infusion, and the 20-minute postinfusion time periods. Significance was reached with a value of $p < 0.05$.

Results

A statistically significant increase ($p < 0.05$) was noted comparing the preinfusion period uterine tone with that observed during the infusion period. Significance ($p < 0.05$) was also found in comparing preinfusion period uterine tone with that of the postinfusion period. The comparison of uterine tone during the infusion period with that of the postinfusion period showed no difference (Fig. 3).

The comparison of uterine activity, expressed in Alexandria units for all study periods failed to show significance at the $p < 0.05$ level (Fig. 4).

Additional observations noted from review of the data showed an average increase in the amniotic fluid infusion of 4.6 ± 1.8 cm for each 250 ml of sterile saline solution infused. The average time required for infusion of 250 ml was 24.6 ± 10.4 minutes. The range of time was 16.2 to 50.7 minutes.

There was a single notable complication observed during this limited evaluation in 10 study subjects. One patient had an episode of uterine hyperactivity soon after the amnioinfusion was begun. This was associated with a prolonged FHR deceleration. Both abnormalities seemingly responsed to intravenous administration of magnesium sulfate. The patient was taken to the operating room for emergency cesarean delivery but on reevaluation the uterus relaxed and the FHR had become normal. Fifteen hours later a 3540 gm male infant was delivered by vacuum extraction with Apgar scores of 9 at both 1 and 5 minutes (Fig. 5).

Comment

In recent years there has been an increasing interest in transcervical intrapartum amnioinfusion. Present indications include prophylaxis and treatment of intrapartum decelerations in both term and preterm gestations,[1-4] dilution and lavage of meconim-stained amniotic fluid,[5,6] and for direct administration of antibiotics within the amniotic cavity in cases of chorioamnionitis.[7] In the limited number of current reports that describe amnioinfusion, little has been reported with regard to potential morbidity to either the mother or fetus.

Clinicians performing amnioinfusion must be aware of the theoretical and potential risks associated with this procedure. When asked by Gimbel[8] about the possibility of cord prolapse, Miyazaki responded that the incidence of this potentially devastating complication was actually one half that seen in vertex presentations during normal labor. We were unable to document other reports of this complication. In our institution over the past year we have noted several instances of fetal dis-

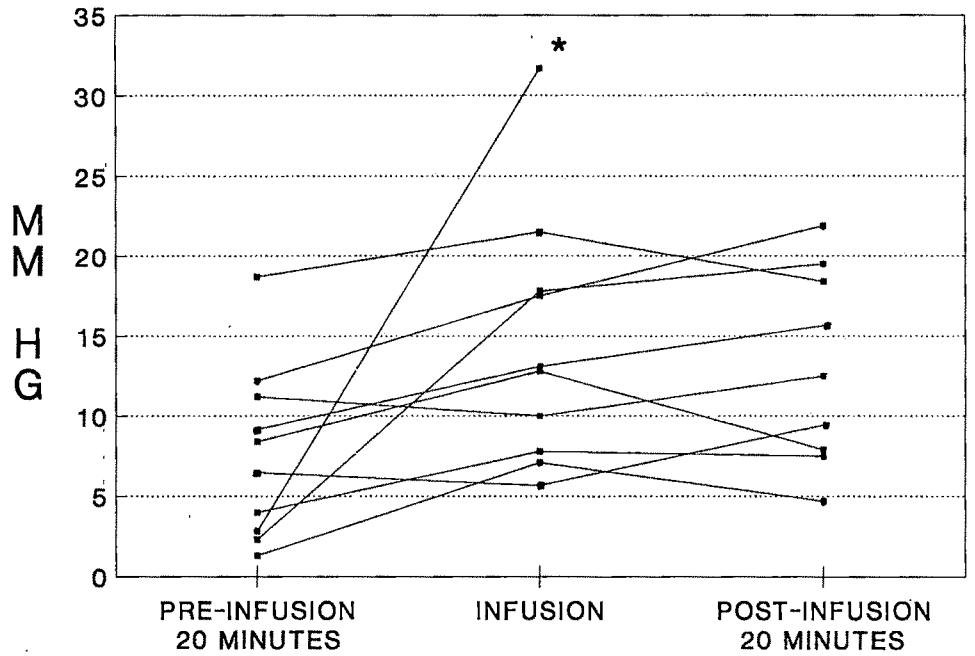


Fig. 3. Basal uterine tone in mm Hg for three study periods. *Asterisk* (*) identifies patient who experienced hypertonic episode followed by fetal distress (see Fig. 5).

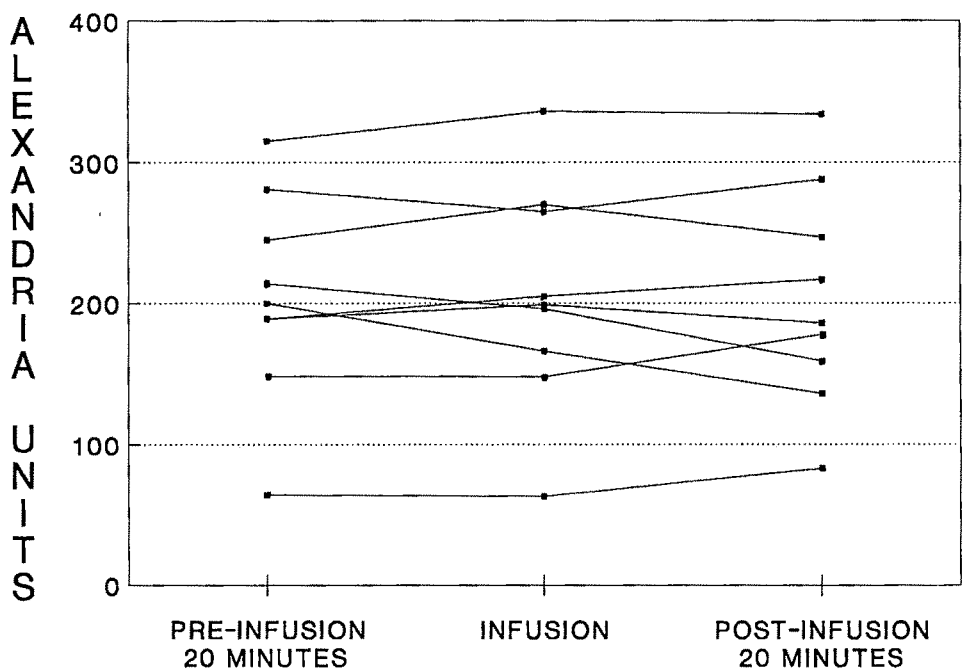


Fig. 4. Uterine activity as expressed in Alexandria units for three study periods.

tress during amnioinfusion. These were associated with a picture that suggests increased uterine activity with clinical palpation. These findings prompted us to better document such occurrences and perhaps define their cause.

Previously Tabor and Maier[11] reported a case of polyhydramnios and elevated uterine pressure during amnioinfusion. According to their report, 4300 ml of normal saline solution was transcervically amnioinfused over a 21-hour period. Some of the fluid leaked out of

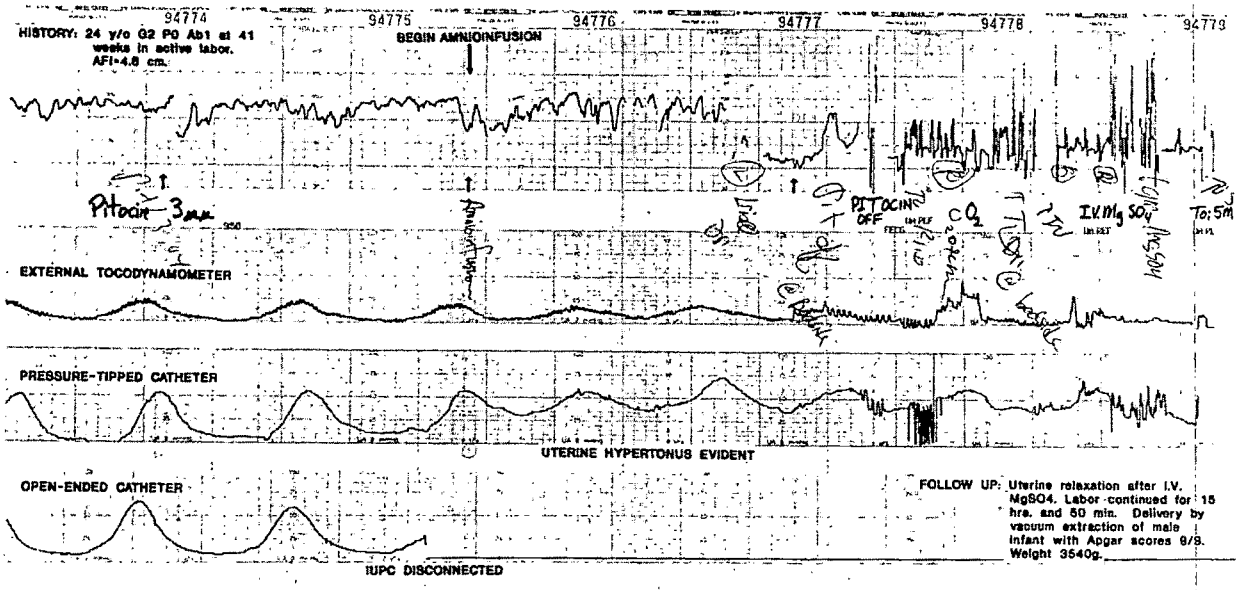


Fig. 5. FHR tracing for patient who experienced uterine hypertonus soon after amnioinfusion was begun. Uterine activity was recorded from external tocodynamometer, pressure-tipped catheter, and open-ended fluid-filled catheter. Patient history and outcome are reported.

the uterus but the majority remained. No estimation of the fluid volume was performed until fetal bradycardia was present. At that time the intrauterine resting pressure had increased to 50 mm Hg from 10 mm Hg before infusion. The FHR returned to normal only after subcutaneous terbutaline administration and removal of 900 ml of fluid. It was speculated that the increased intrauterine pressure had decreased uteroplacental perfusion that resulted in the fetal bradycardia.

Even with a small 250 ml volume of infusate our results show a statistically significant difference in the basal uterine tone when comparing preinfusion with infusion and postinfusion periods. We observed one case in which the uterine tone became excessive. This occurrence in one of 10 patients with the associated abnormal FHR findings is reason for concern and requires further investigative study. To that end an optimal approach to intrapartum amnioinfusion appears to be one in which either two intrauterine pressure catheters or a dual lumen catheter is used. Intrauterine pressure can thus be monitored at all times during the infusion. In addition some objective assessment of amniotic fluid volume should be performed before and at regular intervals after the infusion. In those facilities where such an approach is impractical, amnioinfusion may also be considered beneficial. The minimally acceptable approach in such instances would seemingly demand palpation of the uterus during infusion and close scrutiny of fetal well-being as judged by FHR.

In our institution we currently perform concomitant direct intrauterine pressure monitoring during the amnioinfusion. In addition we measure the amniotic fluid infusion of each patient before and immediately after the amnioinfusion. We attempt to achieve an amniotic fluid infusion of ≥8.0 cm and our infusion volumes are limited. An amniotic fluid infusion ≥8.0 cm was chosen as an objective postinfusion value because it is above our 5.0 cm "at risk" value and it also is well above the range of interobserver error of ±2.0 cm as reported by Rutherford et al.[12] Estimated infusion volume is calculated according to the observations of Strong et al.,[13] substantiated in this limited study, in that 250 ml of infusate will increase the amniotic fluid index by approximately 4 cm. With this method we should minimize the risk of polyhydramnios and overdistention of the uterus.

Further investigation will more accurately define the frequency of complications and probable major benefits for both the fetus and mother of this emerging intrapartum therapy.

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Comparison of umbilical artery pH and 5-minute Apgar score in the low-birth-weight and very-low-birth-weight infant

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The division between "normal" and low Apgar scores is based largely on data obtained from term newborns and may not apply to the premature infant. Umbilical artery pH has been suggested as a better indicator of intrapartum asphyxia. We examined the charts of 558 infants with birth weights ≤2500 gm with respect to umbilical artery pH, 5-minute Apgar scores, and birth weight percentiles. A positive correlation between birth weight and 5-minute Apgar score was noted. No such relationship existed between birth weight and umbilical artery pH. Within birth weight groups, small-for-gestational-age infants have higher Apgar scores and lower umbilical artery pH values than their appropriate-for-gestational age counterparts. (AM J OBSTET GYNECOL 1990;163:818-23.)

Key words: Low birth weight, very low birth weight, acid-base status, Apgar scores

The Apgar score was introduced in the early 1950s to assess, compare, and discuss the results of obstetric practices, types of maternal pain relief, and the effects of resuscitation on the newborn.[1] Although Apgar scores <7 at 5 minutes may implicate the presence of intrapartum asphyxia, most of these infants are vigorous and exhibit no other evidence of an asphyxial insult.[2,3] Umbilical arterial pH may be a more reliable indicator of perinatal asphyxia, but no agreement exists on a value to distinguish normal from abnormal. Most published data on Apgar scores and pH have studied term newborns. Extrapolation of these data to low birth weight (≤2500 gm) and very low birth weight (≤1500 gm) may not be appropriate. We surveyed the charts of all infants delivered at our institution over a 25-month period with birth weights between 500 and 2500 gm to evaluate the relationships between birth weight, 5-minute Apgar scores, and umbilical pH. We subsequently divided the study population into small-for-gestational-age and appropriate-for-gestational-age groups to determine if differences existed between them when either umbilical artery pH or 5-minute Apgar scores were considered.

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6/6/22321

Methods and material

On Oct. 1, 1987, it became standard policy at Denver General Hospital to obtain umbilical cord blood samples on all newborns for blood gas analysis. The samples were obtained by double clamping a section of umbilical cord immediately after delivery of the infant. Blood was drawn into a preheparinized syringe and analyzed within 30 minutes on a Corning 178 blood gas analyzer.

Gestational age was calculated with one of the following: (1) last mentrual period if the patient reported regular menses, had a pelvic examination in the first trimester, and had not used oral contraceptives within 2 months before conception, (2) obstetric ultrasonography if performed before 24 weeks or, if neither of these are available, (3) neonatal assessment of gestational age was determined with the Lubchenco method

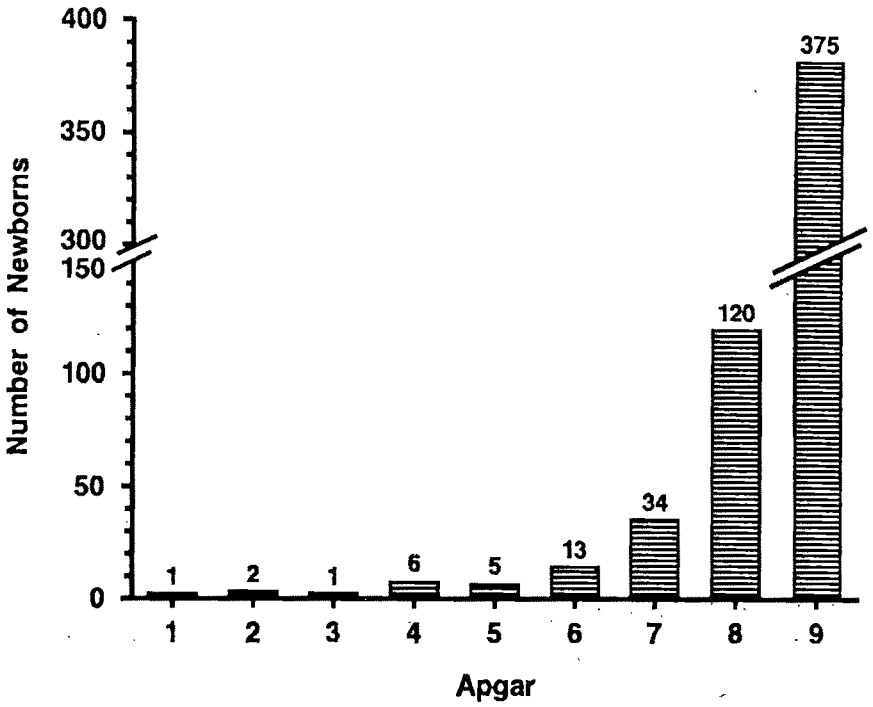


Fig. 1. Number of newborns for each 5-minute Apgar score.

at 1 hour and 24 hours of age.[4] If gestational age derived from the last menstrual period differed by more than 2 weeks from ultrasonographic or neonatal-assessment–based estimates, the latter were accepted as more accurate.

Assessment of birth weight percentiles was based on Denver newborn weight curves.[5]

Apgar scores were assigned to all live-born infants by either pediatric staff or labor and delivery nursing staff.[1]

The charts for all low-birth-weight infants born between Oct. 1, 1987, and Oct. 31, 1989, were reviewed. If a mother was delivered of more than one low-birth-weight infant during the study period, only the first infant was included in the analysis. Twin gestations and infants with chromosomal or major congenital anomalies were excluded.

Statistical analysis was performed with the SAS statistical package. Both umbilical artery pH and Apgar score data were analyzed as continuous variables to detect trends. Statistical tests included simple linear regression, one-way analysis of variance, and Fisher's exact t test. Statistical significance was defined as values of $p < 0.05$.

Results

Five hunded fifty-eight charts were reviewed. No 5-minute Apgar score was recorded in one case and no umbilical artery pH value was recorded for 40 infants. Fig. 1 displays the number of individuals assigned to each Apgar score value. No newborn in the study population was assigned a 5-minute Apgar score of 10. In Tables I and II the distribution of Apgar score and umbilical artery pH among the low-birth-weight and very-low-birth-weight groups is displayed. In Fig. 2, the relationship of 5-minute Apgar score to birth weight is plotted. An analysis of variance demonstrated a significant relationship between birth weight and 5-minute Apgar score ($p < 0.0001$). Mean Apgar scores were calculated for both the low-birth-weight (1501 to 2500 gm, 8.58 ± 0.87) and very-low-birth-weight (500 to 1500 gm, 6.96 ± 1.79) groups and these were significantly different from one another ($p < 0.0001$). In the very-low-birth-weight group, 34.8% of the infants had 5-minute Apgar scores <7 compared with only 2.5% in the low-birth-weight group. This difference was highly significant ($p < 0.0001$). Birth weights in the very-low-birth-weight and low-birth-weight groups were

Table I. Distribution of 5-minute Apgar scores by birth weight groupings

Apgar score at 5 min	*Very low birth weight (501-1500 gm)*	*Low birth weight (1501-2500 gm)*
1	1	0
2	1	1
3	0	1
4	2	4
5	2	3
6	9	4
7	11	23
8	10	110
9	9	366

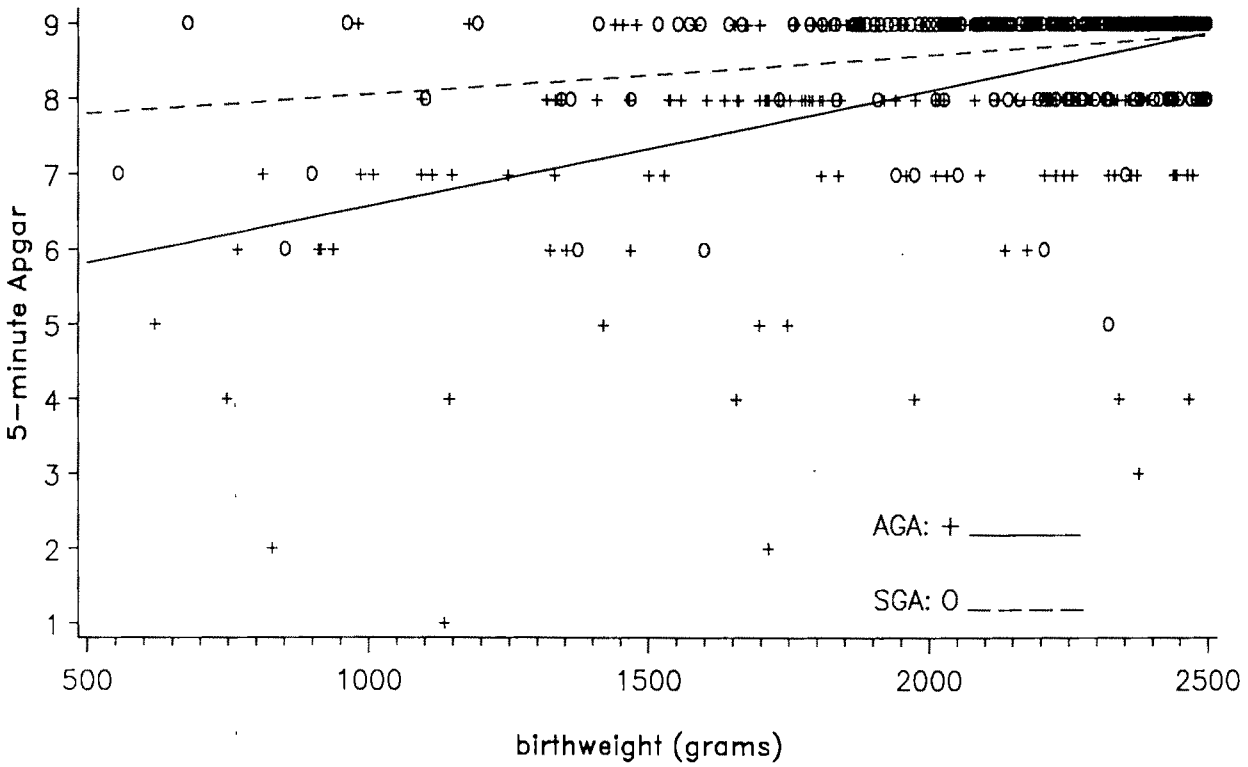


Fig. 2. Scatterplot of 5-minute Apgar score versus birth weight in 558 newborns. The regression lines for appropriate-for-gestational-age and small-for-gestational-age cases are calculated with the following equations: Apgar 5 (appropriate-for-gestational-age) = 5.05 + (0.00154 × birth weight); Agpar 5 (small-for-gestational-age) = 7.54 + (0.000529 × birth weight).

Table II. Distribution of umbilical artery pH by birth weight groupings

Umbilical artery pH	*Very low birth weight (501-1500 gm)*	*Low birth weight (1500-2500 gm)*
≤7.00	0	1
7.01-7.05	0	1
7.06-7.10	1	3
7.11-7.15	2	3
7.16-7.20	2	20
7.21-7.25	4	73
7.26-7.30	9	124
7.31-7.35	6	135
7.36-7.40	9	75
7.41-7.45	9	29
7.46-7.50	0	11
≤7.51	0	1

then subdivided into small-for-gestational-age and appropriate-for-gestational-age groups. Mean Apgar scores were calculated and compared (Fig 3). The differences between mean Apgar scores in the small-for-gestational-age and appropriate-for-gestational-age groups were highly significant ($p < 0.006$) in both the last menstrual period and very-low-birth-weight groups. Umbilical artery pH values were then plotted against birth weight (Fig. 4). Linear regression analysis revealed no relationship between the two variables. When umbilical artery pH in newborns with 5-minute Apgar scores <7 were compared with infants with scores ≥7 (7.28 ± 0.13, vs 7.31 ± 0.07) no statistical difference was shown. Linear regression analysis was also used to describe the relationships between birth weight and both umbilical artery pH and 5-minute Apgar score in infants categorized as either small for gestational age or appropriate for gestational age (Figs. 2 and 4). Significant intergroup differences (small for gestational age versus appropriate for gestational age) were demonstrated in the relationship of umbilical artery pH and 5-minute Apgar scores to birth weight when both the slopes and the elevations of the two lines were compared ($p < 0.05$).

Comment

Of the five categories assessed in the Apgar score, four (heart rate, respiratory rate, reflex irritability, and muscle tone) are dependent on the maturity of both the central nervous and musculoskeletal systems for maximal score assignment.[1] During the last 3 months of fetal life continuous maturation of the cerebral cortex results in improvements in muscle tone and the appearance of reflexes used in Apgar score determinations.[6] Respiratory patterns constantly change dur-

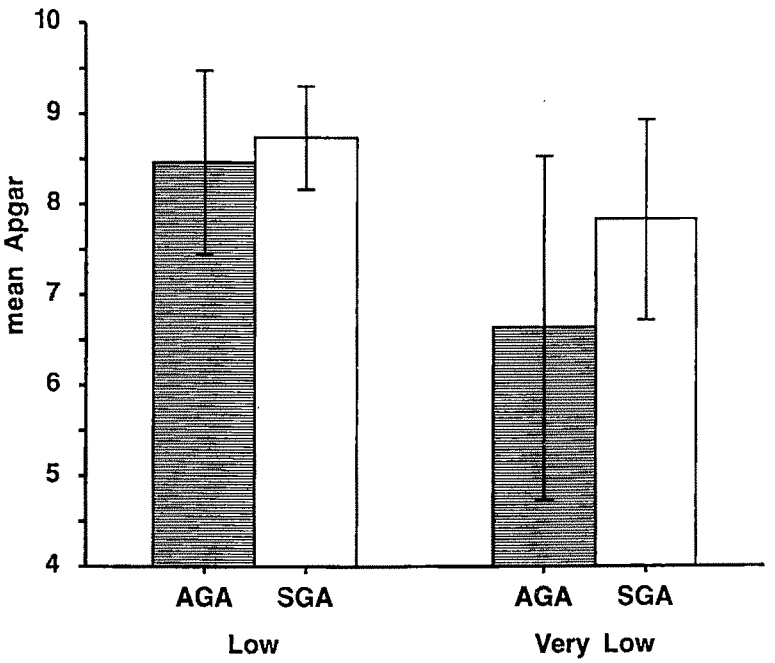


Fig. 3. Comparison of Apgar scores at 5 minutes (mean ± SD) in appropriate-for-gestational-age and small-for-gestational-age newborns in low- and very-low-birth-weight groups.

ing the last 2 months of fetal life, and periodic breathing and short periods of apnea account for a large proportion of respiratory activity. Respiratory patterns characteristic of term newborns are rarely observed before 23 weeks.[7, 8]

Several investigators have demonstrated the frequent occurrence of low Apgar scores in the nonacidemic premature infant.[2, 9-13] An immature central nervous system, musculoskeletal system, or both, rather than the presence of significant acidosis, appears to be the most important factor in the increased incidence of Apgar scores <7 in these infants. Not only did we confirm this relationship between low birth weight and Apgar scores <7 but we also expanded on it. We demonstrated a linear relationship between 5-minute Apgar scores and birth weight in newborns with birth weights <2500 gm. When we divided the study group into low-birth-weight (1501 to 2500 gm) and very-low-birth-weight groups (500 to 1500 gm) we found the influence of birth weight to be most clinically significant in the newborns with birth weights <1500 gm. Although other investigators have noted that 50% to 70% of very-low-birth-weight infants and from 8% to 18% of low-birth-weight infants have 5-minute Apgar scores <7,[12, 13] we found the incidence of these low Apgar scores to be significantly less than previously reported (very low birth weight, 34.78%; low birth weight, 2.54%). This finding may reflect a higher proportion of small-for-gestational-age or growth-retarded individuals in our very-low-birth-weight and low-birth-weight populations.

When compared with infants of similar low birth weight, we found that infants categorized as small-for-gestational-age had significantly higher 5-minute Apgar scores than their appropriately grown counterparts. Although debate exists regarding the use of the *t* test and analysis of variance to analyze Apgar score data, recent evidence appears to support its accuracy in this context (Bottoms S, unpublished data). We speculate that this is caused by a tendency of these infants to be older, growth-retarded, or both. Delivery of the very small infant often occurs in a setting in which little or no prenatal care has been obtained. These pregnancies are often complicated by the presence of obstetric and maternal conditions that are associated with uteroplacental insufficiency, subsequent intrauterine growth retardation, and delivery of a small-for-gestational-age infant. Neurologic investigations of low-birth-weight newborns led Amiel-Tison[6] to conclude that those infants who appeared to be growth retarded were more neurologically developed than was expected on the basis of birth weight alone. Growth retardation leads to a compromise in birth weight, but not at the expense of central nervous system or musculoskeletal system development. The differences between Apgar scores in these two groups (small-for-gestational-age group versus appropriate-for-gestational-age group) were most clinically apparent in the very-low-birth-weight group (Fig. 2). These observations reinforce the importance of central nervous and musculoskeletal system maturity rather than acidemia on 5-minute Apgar scores in the majority of small premature infants.

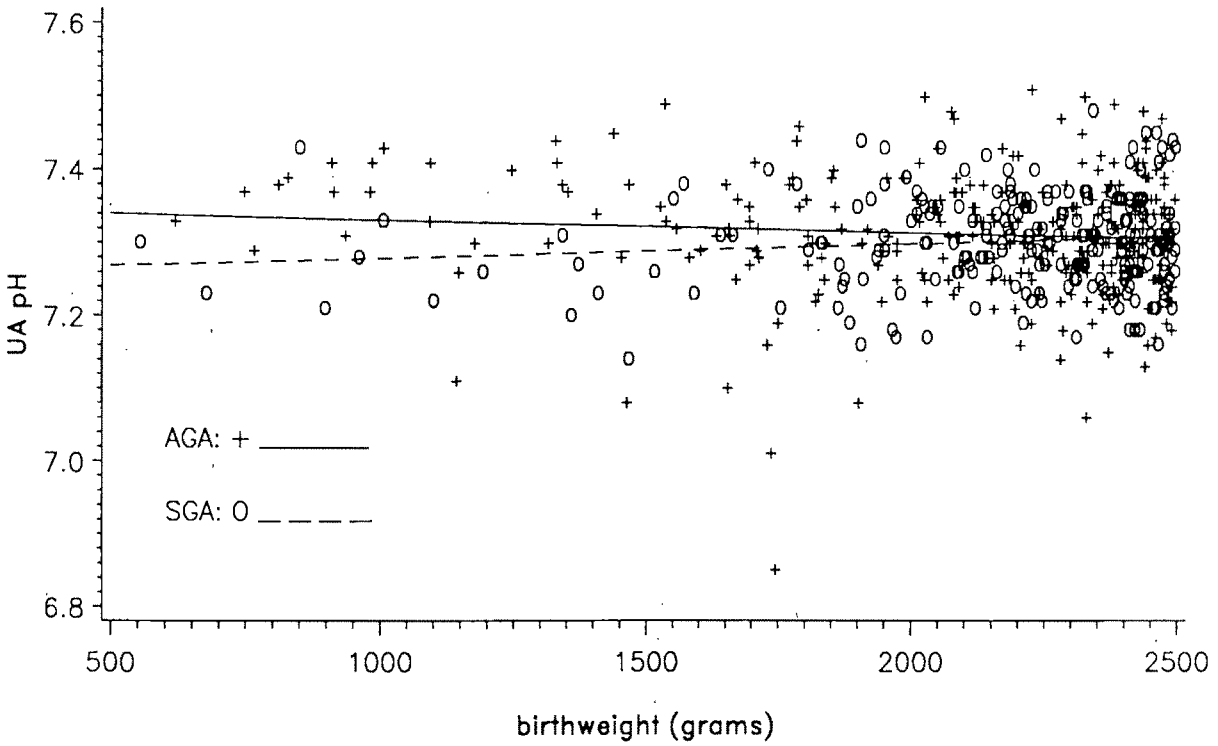


Fig. 4. Scatterplot of umbilical artery pH versus birth weight in 558 newborns. The regression lines for appropriate-for-gestational-age and small-for-gestational age cases are calculated with the following equations: Umbilical artery pH (appropriate-for-gestational-age) = 7.35 − (0.0000171 × birth weight); umbilical artery pH (small-for-gestational-age) = 7.26 + (0.0000204 × birth weight).

Several recent studies have evaluated umbilical artery pH in infants with birth weights ≤2500 gm. Umbilical artery pH was not found to vary with either rising birth weight or lower Apgar scores.[2, 11, 14-16] We also found no change in umbilical artery pH values over the low-birth-weight spectrum (Fig. 4). Sampling of the umbilical artery rather than the umbilical vein appears to be a more sensitive method to assess fetal acid base status because umbilical artery pH values are influenced by umbilical venous pH and fetal metabolism, whereas umbilical venous blood pH values often reflect the presence of either maternal acidosis or alkalosis.[14] Yudkin et al.[14] demonstrated lower umbilical venous pH values but no difference in umbilical artery pH values when low-birth-weight small-for-gestational-age infants were compared with the remaining low-birth-weight population. Although we only sampled the umbilical artery, we found significantly lower pH values in the small-for-gestational-age infants when compared with their appropriate-for-gestational-age counterparts. Our findings are consistent with those of Nickolaides et al.[17] in which acid-base analysis of umbilical artery blood was obtained by cordocentesis in small-for-gestational-age and appropriate-for-gestational-age infants.

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Preterm delivery: A risk factor for retained placenta

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The purpose of this study was to determine whether preterm delivery, with and without intraamniotic infection, is a risk factor for retained placenta. This complication occurred more frequently in women with preterm vaginal delivery than in women with term vaginal delivery (9.1% [21/231] vs 1.1% [6/561]; $p < 0.00001$; odds ratio = 9.25). There was no significant difference in the prevalence of retained placenta between women with preterm labor and intact membranes and those with preterm premature rupture of membranes (8% [10/125] vs 10.4% [11/106]; $p \geq 0.05$). A positive amniotic fluid culture or clinical chorioamnionitis was not associated with a higher incidence of retained placenta. This study indicates that preterm delivery is associated with an increased risk of complications of the third stage of labor. (Am J Obstet Gynecol 1990;163:823-5.)

Key words: Placenta, preterm labor, third stage of labor, intraamniotic infection, chorioamnionitis, parturition, retained placenta, prematurity

There is a paucity of information concerning complications of the third stage of labor in women who deliver preterm neonates. During the course of our studies of preterm labor, we made the observation that the incidence of retained placenta was higher in preterm deliveries than in term parturients. Because one of every five preterm neonates is delivered to a woman with a positive amniotic fluid culture for microorganisms,[1] we hypothesized that retained placenta may be associated with microbial invasion of the amniotic cavity. The purpose of this study was to determine whether preterm delivery, with and without intraamniotic infection, is a risk factor for retained placenta.

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6/6/22594

Material and methods

A retrospective study was undertaken to determine the frequency of retained placenta in women with preterm delivery. Criteria for inclusion into the study were: (1) singleton pregnancy; (2) preterm delivery (20 to 36 weeks); (3) vaginal delivery; and (4) amniocentesis performed on admission for microbiologic studies of the amniotic fluid. The study included patients who delivered in a 25-month period between Jan. 1, 1987, and Feb. 28, 1989, at Yale–New Haven Hospital. Patients were classified into two groups: (1) those with preterm labor and intact membranes and (2) those with preterm

Table I. Demographic characteristics of population

	Preterm labor, intact membranes	*Preterm labor with PROM*	*Control group*
No. of patients	125	106	561
Maternal age (yr)*	28.5 ± 13.5	28 ± 12	27.5 ± 13.5
Gravidity			
Primigravid	28	25	97
Multigravid	97	81	464
Parity			
Primiparous	53	51	258
Multiparous	72	55	303
Gestational age at delivery (wk)†	28 ± 8 (22-36)	30 ± 8 (22-36)	39 ± 2 (37-43)

*Data are mean ± SD.
†Data are mean ± SD and range.

Table II. Prevalence of retained placenta in patients with preterm labor and positive or negative amniotic fluid cultures

	No. of patients	*Patients with retained placenta*	
		No.	*%*
Preterm labor with intact membranes	125	10	8
Positive culture	34	5	14.7
Negative culture	91	5	5.5
Preterm labor with PROM	106	11	10.37
Positive culture	49	6	12.24
Negative culture	57	5	8.8
Control group	561	6	1.1

premature rupture of membranes (PROM). Amniotic fluid was cultured for aerobic and anaerobic bacteria, *Mycoplasma hominis*, and *Ureaplasma urealyticum* as previously described.[2] An intraamniotic infection was defined as the presence of a positive amniotic fluid culture. Clinical chorioamnionitis was diagnosed by the criteria previously described by Gibbs et al.[3] Patients with premature labor, intact membranes, and negative Gram stain examinations of amniotic fluid were treated with tocolytic agents (ritodrine, terbutaline, or magnesium sulfate). Expectant management was undertaken for patients with preterm PROM and a negative Gram stain. Patients with positive Gram stain examinations of amniotic fluid were treated with parenteral antibiotics, and labor was induced.

The standard management of the third stage of labor in our institution is to wait for signs of placental separation before attempting to deliver the placenta. A retained placenta is defined as the lack of spontaneous separation and delivery of the placenta 30 minutes after completion of the second stage of labor. Management of retained placenta consists of manual removal with the patient under general or regional anesthesia. A curettage is performed when there is a suspicion of retained placental fragments.

To determine whether the incidence of retained placenta in preterm gestation was different from that observed after term delivery, a control group consisting of consecutive term vaginal deliveries occurring between Jan. 1, 1989, and Feb. 28, 1989, was studied.

Results

During the study period, there were 231 preterm vaginal deliveries; 125 patients had preterm labor with intact membranes, and 106 had preterm PROM. The control group consisted of 561 patients with vaginal delivery at term.

Table I displays the demographic characteristics of women with preterm labor and intact membranes, women with preterm PROM, and the term control group. No significant differences were detected in any of these parameters among groups. The mean gestational age in the control group was greater than in the study groups.

The incidence of retained placenta was significantly higher in women with preterm vaginal delivery than in women with term vaginal delivery (9.1% [21/231] vs 1.1% [6/561]; $p < 0.00001$; odds ratio = 9.25) There was no significant difference in the incidence of retained placenta between women with preterm labor and intact membranes and those with preterm PROM (8% [10/125] vs 10.4% [11/106]; $p \geq 0.05$).

To determine whether the presence or absence of microbial invasion of the amniotic cavity was a risk factor for retained placenta, analysis was conducted after stratification for amniotic fluid culture results. A positive amniotic fluid culture was not associated with a higher incidence of retained placenta in either of the two groups (preterm labor with intact membranes or preterm PROM) (Table II). Furthermore, a difference in the prevalence of retained placenta between patients with positive and negative amniotic fluid cultures could

not be detected even after patients with preterm labor and intact membranes and patients with preterm PROM were added ($\chi^2 = 1.98$; $p = 0.15$). This study has a power of 80% to detect a difference in proportions between the groups of 10%.

A similar analysis was conducted to establish whether clinical chorioamnionitis was associated with an increased incidence of retained placenta in either group. No statistically significant differences were observed (Table III).

Table III. Prevalence of retained placenta in patients with preterm labor with or without clinical chorioamnionitis

	No. of patients	*Retained placenta*	
		Yes	*No*
Preterm labor with intact membranes			
Clinical chorioamnionitis	5	1	4
Without clinical chorioamnionitis	120	9	111
Preterm labor with PROM			
Clinical chorioamnionitis	15	2	13
Without clinical chorioamnionitis	91	9	82

Comment

The results of this study clearly indicate that the rate of retained placenta is higher in women with preterm vaginal delivery than in women with term vaginal delivery. The incidence of retained placenta in our term control group is consistent with the rate reported in the literature,[4, 5] and therefore our results cannot be attributed to an underestimation of the rate of retained placenta in the control group at term.

Why is preterm delivery associated with a higher incidence of retained placenta? Our first inclination was to attribute this to intrauterine infection. Inflammation at the placental site could lead to abnormalities of the third stage of labor. Our data do not support this hypothesis. However, a limitation of our study is the utilization of amniotic fluid microbiology as an index of intrauterine infection. This method cannot identify intrauterine infections limited to the decidua.

Several alternative explanations may be considered. The currently used definition of retained placenta (failure to deliver after 30 minutes of fetal expulsion) was conceived for the management of the third stage of term labor. There is little information regarding the normal duration of the third stage of preterm labor and delivery. In a recent study examining the duration of placental separation in women undergoing midtrimester prostaglandin E_2 pregnancy terminations, only 37.5% of placentas were delivered spontaneously within 30 minutes.[6] Thus the normal duration of the third stage of labor may be longer in the preterm than in the term gestation. If this is the case, intervention after 30 minutes may be premature and increase the risk for maternal morbidity. An observational study is required to determine the normal duration of the third stage of preterm labor.

The two mechanisms involved in physiologic placental separation are uterine contractions and the formation of a retroplacental clot. As the preterm placenta covers a relatively larger uterine surface than the term placenta, the detachment of a preterm placenta may require more uterine work and time. There are no available data regarding the intensity of uterine contractions during the third stage of preterm labor.

A retained placenta requires manual removal and often a curettage with the patient under anesthesia. These procedures increase the risk for maternal complications, including uterine perforation, hemorrhage, infection, and uterine synechia.[7, 8] In conclusion, preterm delivery increases the risk not only of perinatal mishap but also of maternal complications.

We gratefully acknowledge the assistance of Carol Brekus, MSN, CNM, and Valerie W. Kraemer, MFA.

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Fetal umbilical artery Doppler response to graded maternal aerobic exercise and subsequent maternal mean arterial blood pressure: Predictive value for pregnancy-induced hypertension

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Predictive tests for the identification of women at high risk of the development of preeclampsia are critical to allow the most appropriate preventive measures. Preeclampsia is a vasospastic condition of pregnancy characterized by early and enhanced vascular reactivity to endogenous pressor agents. Exercise tolerance testing with cycle ergometry to induce hemodynamic response measured with duplex Doppler A/B ratio of the umbilical artery could unmask latent vascular pressor hypersensitivity. Our prospective cohort study was designed to test the efficacy of the American College of Obstetricians and Gynecologists exercise in pregnancy guidelines for the low-risk atheletic, physically active, or sedentary patient. The pattern of fetal response to material exercise testing at 28 weeks' gestation was compared with subsequent maternal mean arterial blood pressure and the development of pregnancy-induced hypertension and preeclampsia. Doppler A/B ratio during the recovery period was assessed as below baseline (18) or elevated above resting baseline values (12). Third-trimester blood pressure pattern was assessed to be elevated in 11 patients, 10 of whom had elevated recovery A/B ratios. The Fisher exact test results were ($p = 0.00002$) positive predictive value, 83%; negative predictive value, 94%; sensitivity, 91%; and specificity, 89%. Preeclampsia developed in four patients; all had elevated recovery A/B ratios. Fisher exact test results were ($p = 0.01806$) positive predictive value, 33%; negative predictive value, 100%; sensitivity, 100%; and specificity, 69%. (Am J Obstet Gynecol 1990;163:826-9.)

Key words: Fetal exercise tolerance testing, Doppler velocimetry, preeclampsia

Valid predictive tests for the identification of gravida at high risk of the development of preeclampsia are essential to all efforts of prevention in this critical unresolved area of perinatology. Preeclampsia is a vasospastic condition of pregnancy characterized by early and enhanced vascular reactivity to endogenous pressor agents.[1-5] This heightened vascular tonicity, or reactivity, may be responsible for the early elevations in mean arterial blood pressure (MAP) observed in those gravidae in whom preeclampsia is destined to develop.[6] Doppler flow measurements may offer biophysical assessment of the vascular tone before changes in blood pressure.[7-9] After we have observed the increased immediate recovery phase midumbilical artery A/B ratio response in an obese subject who went on to manifest elevated MAP and subsequently mild preeclampsia (unpublished observation), we formulated the following hypothesis. Exercise tolerance testing (at 60% of the maximum volume of oxygen used) with cycle ergometry to induce hemodynamic response measured with duplex Doppler A/B ratio of the umbilical artery could unmask latent vascular pressor hypersensitivity, and this would be independent of the level of maternal physical fitness.

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6/6/22621

Material and methods

Volunteers were recruited from our prenatal clinics at Duke University Medical Center. All candidates for the study had a baseline ultrasonographic examination (GE RT 2400) to confirm estimated gestational age, and to exclude cases of multiple gestation, placenta previa, intrauterine growth retardation, and fetal anomalies. Multiparous subjects had no prior history of growth retardation, stillbirth, premature labor, or preeclampsia. Informed consent was obtained in accordance with Duke University Medical Center Institutional Review Board approved protocol. This prospective cohort study design compared the immediate post exertion, or recovery phase, umbilical artery Doppler A/B ratios at 28 weeks' gestation exercise tolerance testing with subsequent maternal MAP and the development of pregnancy-induced hypertension and preeclampsia. Subjects were 30 volunteers from the experimental

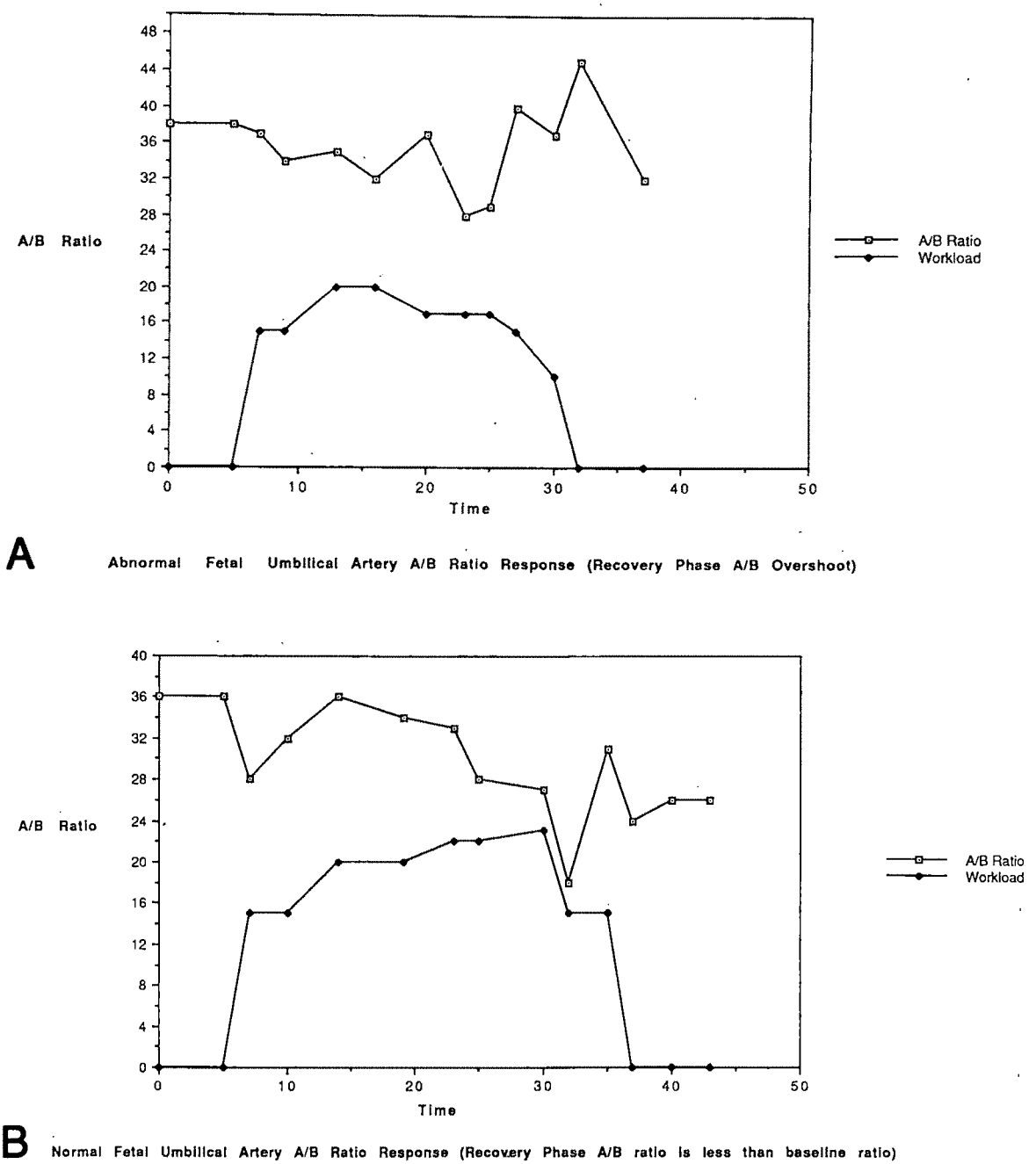


Fig. 1. Fetal midumbilical artery Doppler A/B ratio response to graded maternal aerobic exercise.

study previously presented (Fetal umbilical artery Doppler response to graded maternal aerobic exercise. Presented at the Armed Forces District/American College of Obstetricians and Gynecologists, Denver, Colorado, October 1988, and the Ninth Annual Meeting of the Society of Perinatal Obstetricians, New Orleans, Louisiana, February 2-4, 1989) who were followed-up throughout their pregnancy. Of the 30 subjects, 22 were nulliparous. The distribution of physical fitness category defined by lifestyle and the Canadian Home Fitness Test among the 30 subjects was nine athletes, 16 physically active, and five sedentary.

Exercise tolerance tesing used a FITRON isokenetic cycle ergometer and adhered to American College of Obstetricians and Gynecologists Technical Bulletin guidelines for safe exercise during pregnancy and were generally in the mild-moderate aerobic range (60% of the maximum volume of oxygen used). Ultrasonographic surveillance (Acuson 128, Acuson, Mountain View, Calif.) was continuous throughout standard aerobic exercise and included observation of fetal heart rate, breathing, movement, and pulsed duplex Doppler A/B ratio of the midumbilical cord artery measured serially during all exercise phases in the

Table I. Summary of fetal exercise tolerance Doppler A/B response at 28 weeks' gestation and maternal blood pressure at term

Maternal fitness	*Recovery A/B overshoot*	*Elevated MAP at term*	*Preeclampsia*
Athlete (n = 9)			
Nulliparous	2/6	2/6	1/6
Multiparous	0/3	0/3	0/3
Active (n = 16)			
Nulliparous	6/13	6/13	2/13
Multiparous	0/3	0/3	0/3
Sedentary (n = 5)			
Nulliparous	1/1	1/1	1/1
Multiparous	3/4	2/4	0/4
TOTAL (n = 30)			
Nulliparous	9/20	9/20	4/20
Multiparous	3/10	2/10	0/10

Table II. Association of fetal Doppler A/B recovery overshoot for subsequent MAP elevation and preeclampsia

Doppler response	*Elevated MAP*	*Preeclampsia*
Recovery normal (18)	1/18	0/18
Recovery elevated (12)	10/12	4/12

Table III. Effectiveness of fetal exercise tolerance Doppler response to predict elevated MAP and preeclampsia

Diagnostic values	*Elevated MAP*	*Preeclampsia*
Fisher exact test	p = 0.00002	p = 0.01806
Sensitivity (%)	91	100
Specificity (%)	89	69
Positive predictive value (%)	83	33
Negative predictive value (%)	94	100

seated position; 5-minute baseline, 5-minute warm-up, 15- to 20-minute sustained, 5-minute cool-down, and 5- to 10-minute recovery. Maternal heart and respiratory rate response to exercise determined the exact time and duration of each phase to achieve 15 minutes at 140 beats/min recommended by the American College of Obstetricians and Gynecologists. Serial ultrasonographic evaluations for growth, amniotic fluid volume, and fetal well-being were performed monthly until delivery.

The normal exercise tolerance testing umbilical artery Doppler A/B ratio response is to decrease during and after exertion(Fig. 1, *A*). This suggests less resistance to flow, less impedance, and normal vascular reactivity. Abnormal exercise tolerance testing umbilical artery Doppler A/B ratio response is to increase above the resting baseline, suggesting greater vascular reactivity in response to exertion (Fig. 1, *B*). The immediate post exertion recovery phase A/B ratios were determined to be normal or elevated above the resting baseline A/B ratio values, each subject serving as her own control. The values obtained at the 28-week exercise tolerance testing were compared with subsequent maternal MAP values.

(MAP = [Systolic blood pressure + (2 × Diastolic blood pressure)] / 3) is defined as abnormal if >105 mm or if increased >20 mm compared with first-trimester baseline values (American College of Obstetricians and Gynecologists Committee on Terminology). The obstetric records were reviewed by an observer blinded to exercise tolerance testing umbilical artery Doppler A/B response to obtain diagnoses of pregnancy-induced hypertension, preeclampsia, and delivery outcome. All subjects registered for prenatal care in the first trimester. The initial clinic MAP (first three visits) and the late third-trimester MAP (last three visits) were calculated and used in the comparison.

Nonparametric statistical methods were used, (χ^2 or the Fisher extact test), and predictive values, sensitivity, and specificity of exercise tolerance testing umbilical artery Doppler A/B as a screening test were determined.

Results

No maternal injuries or fetal bradycardia, distress, or tachypnea occurred during the exercise tolerance testing. All subjects' resting baseline Doppler A/B ratios were normal for gestational age. Each subject served as her own control for the definition of abnormal response, recovery overshoot. Doppler A/B ratio during the recovery phase was assessed to be below resting baseline in 18 of 30 subjects and elevated above resting baseline in 12 of 30 subjects. Third-trimester maternal blood pressure was assessed to be elevated in 11 subjects, 10 of whom had elevated recovery A/B ratio response to exertion. Preeclampsia developed in four subjects; all had elevated recovery A/B ratios.

Table I presents the data in summarized form according to maternal fitness and parity. All cases of preeclampsia occurred in nulliparous subjects. The elevated exercise tolerance testing umbilical artery Doppler A/B response and increased MAP and preeclampsia occurred in all fitness categories. Physical fitness may be unrelated to vascular pressor sensitivity. The statistical analyses of the association of exercise tolerance testing umbilical artery Doppler A/B ratio recovery overshoot to maternal MAP (Fisher exact test, p = 0.00002) and pregnancy-induced hypertension

and preeclampsia (Fisher exact test, $p = 0.01806$) are presented in Tables II and III, respectively. The predictive value of the exercise tolerance testing umbilical artery Doppler A/B ratio unmasking subsequent increased MAP is positive predictive value 83%, negative predictive value 94%, sensitivity 91%, and specificity 89%. The predictive value of the exercise tolerance testing umbilical artery Doppler A/B ratio for preeclampsia is positive predictive value 33%, negative predictive value 100%, sensitivity 100%, and specificity 69%.

Comment

The statistical analyses of the association of altered umbilical artery A/B ratio response to maternal exertion and MAP reflect the pathophysiology of preeclampsia and the physiologic response to exercise in the gravid woman. Exercise is known to induce the release of endogenous vasopressor agents such as norepinephrine, epinephrine and atrial natriuretic factor.[10] The recovery phase of aerobic exercise is particularly a period of enhanced hyperdynamic response to the oxygen debt and the lactic acid load released from the working muscles and the increased catecholamine levels.[10, 11] The response of atrial natriuretic factor, vasopressin, and angiotensin II in the gravid are less clear in human research. Regardless of the specific agent(s) responsible it is clear that there is a generalized increase in endogenous vasoactive activity during and immediately after exercise.

Preecalmpsia is associated with alteration in placental, decidual, and umbilical artery prostanoid metabolism favoring vasospasm—prostacyclin versus thromboxane imbalance.[12, 13] This thesis seems to be strongly supported by the success of aspirin therapy in the prevention of preeclampsia in a cohort of angiotension II hypersensitive gravidae.[14] The final pathway of the pathophysiology of preeclampsia would seem to be related to the endothelial hypersensitivity to the endogenous vasopressors (renin, angiotensin II, artrial natriuretic factor)[15-18] because of this altered prostanoid metabolism.[19] This alteration of vascular reactivity is measurable with existing Doppler ultrasonographic technology.[20] The latent hypersensitivity that we measure during the immediate recovery phase could be unmasked through the induction of endogenous vasoactive agents in response to maternal exertion. Fetal exercise tolerance testing (exercise tolerance testing umbilical artery Doppler) may serve as a practical predictive test for such vascular hypersensitivity. Larger numbers of study patients are necessary to determine the clinical usefulness of this diagnostic tool.

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The Shirodkar operation: A reappraisal

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Sixty-six cerclages were performed by one surgeon in 46 patients with documented cervical incompetence. The mean operative blood loss was 25 ml, and the mean operating time was 18 minutes with no postoperative morbidity. Fifty-five of the pregnancies were carried for at least 37 weeks, eight were delivered before 37 weeks, and three are continuing. Six of the eight preterm deliveries were a result of factors unrelated to cervical incompetence. The two remaining preterm births were probably also unrelated because one occurred 8 days after emergent cerclage placement and the other occurred 12 weeks after the procedure, both as a result of premature rupture of membranes. There were no cesarean deliveries related to the Shirodkar suture. The efficacy of the procedure was demonstrated by a corrected perinatal survival rate of 100% and term delivery of 88%. (Since this article was written all three of the undelivered patients were delivered of infants after 37 weeks' gestation for a term delivery rate of 88% with 100% neonatal survival.) (Am J Obstet Gynecol 1990;163:830-3.)

Key words: Shirodkar procedure, cervical cerclage, incompetent cervix

Operative correction of the incompetent cervix has been debated since the 1950s when Lash and Lash,[1] Shirodkar,[2] and McDonald[3] described their techniques. The two most commonly used operations are the Shirodkar and McDonald cerclages. However, the Shirodkar procedure is particularly useful in cases with old lacerations or gross anatomic defects of the cervix and therefore is the most universally applicable. Currently there is a lack of exposure to the Shirodkar operation in obstetric training because it is not frequently performed. This retrospective study summarizes one author's (B. K. Y.) experience with the Shirodkar operation and suggests further consideration of this procedure.

Material and methods

During the period between 1974 and 1989 46 patients underwent 66 Shirodkar procedures. All patients had a history of midtrimester fetal loss with painless cervical dilatation. All patients except one had a workup between pregnancies demonstrating at least one objective test (hysterosalpingogram, hysteroscopy, or passage of a no. 8 Hegar dilator), thus confirming the diagnosis of incompetent cervix. There was visible cervical dilatation with bulging membranes in patients who had emergency cerclage, including the one patient with a positive history but no diagnostic work-up.

The operation was performed electively between 13 and 18 weeks' gestation and emergently as late as 24 weeks. The procedure was done with the patient under regional anesthesia; only two patients required general anesthesia for failed epidural.

The cerclage was performed after the method described by Shirodkar[2] with slight modification as follows. The anterior and posterior lips of the cervix are grasped with sponge forceps. A 1 cm transverse incision is made with scissors anteriorly, at the cervicovesical junction, and the bladder is advanced cephalad, past the level of the internal os, using blunt dissection (Fig. 1). A similar incision is made posteriorly and the peritoneum is bluntly reflected past the level of the internal os (Fig. 2) off the cervix. Instead of a strip of fascia lata from the patient's thigh, as described by Shirodkar, a 5 mm Mersilene band doubly armed with curved needles is placed submucosally from posterior to anterior on each side of the cervix at the level of the internal os and is tied anteriorly (Fig. 3). No anchoring sutures are used and the internal os is closed to <1 cm diameter by tying the Mersilene band. The vaginal mucosa is closed at both incisions with a running locked 00-chromic suture, burying the Mersilene band and achieving hemostasis. No packs or drains are used and no catheterization is necessary.

Postoperatively the patients are maintained on bed rest with bathroom privileges and prophylactic tocolytics are given for 12 to 24 hours. Thereafter their activity is limited only by the usual pregnancy restrictions. The suture is removed with the patient under

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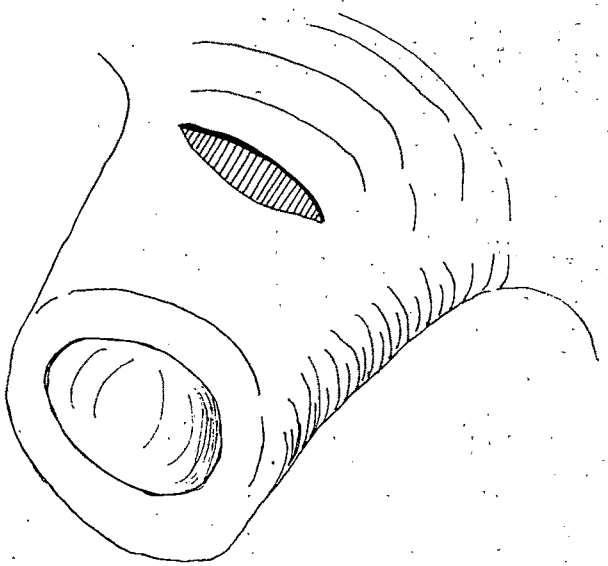


Fig. 1. Anterior incision.

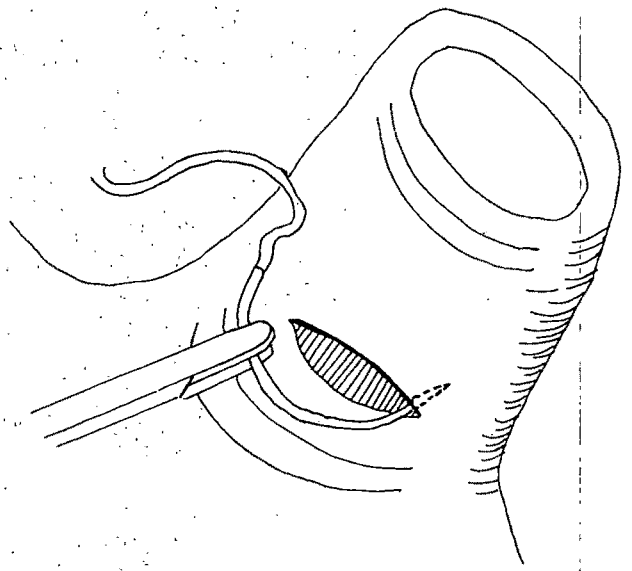


Fig. 2. Posterior incision and needle being passed.

epidural anesthesia at the onset of labor by incising the mucosa over the knot and cutting the Mersilene band. The mucosa is not sutured unless there is significant bleeding, which rarely occurs.

Results

In this series 46 patients underwent 66 Shirodkar procedures. Only one procedure was performed during a given pregnancy (none required repetition), but some patients were treated for more than one pregnancy. The average gestational age at the time of the cerclage was 15.3 weeks. Mean estimated blood loss was 25 ml (range, 10 to 50 ml), and mean operative time was 18 minutes (range, 12 to 35 minutes).

Before their first cerclage procedure in this study the patients had a total of 94 pregnancies beyond the first trimester with a fetal survival rate of 35%. In our series 55 of the 66 treated pregnancies were carried to 37 weeks or more. Eight patients were delivered before 37 weeks and three women had continuing pregnancies with gestational age >32 weeks at the time of this report (Fig. 4). The preterm births consisted of one at 30 weeks with abruptio placentae, one at 34 weeks because of hemorrhage secondary to placenta previa, one at 34 weeks by cesarean section for severe preeclampsia, three intrauterine fetal deaths between 16 and 32 weeks, and two with spontaneous amniorrhexis at 17 and 26 weeks. Thus only the last two of these preterm deliveries might be attributed to cervical incompetence. However, it is unlikely that even these losses were related to cervical incompetence because one occurred 8 days after emergent correction at 3 cm dilatation and necessitated use of prostaglandin E_2 suppositories to empty the uterus, and the other occurred 12 weeks after the cerclage with ruptured membranes and labor. Consequently the corrected outcome, excluding fetal death and preterm deliveries unrelated to cervical incompetence, was 100% of patients delivered at or beyond 37 weeks' gestation.

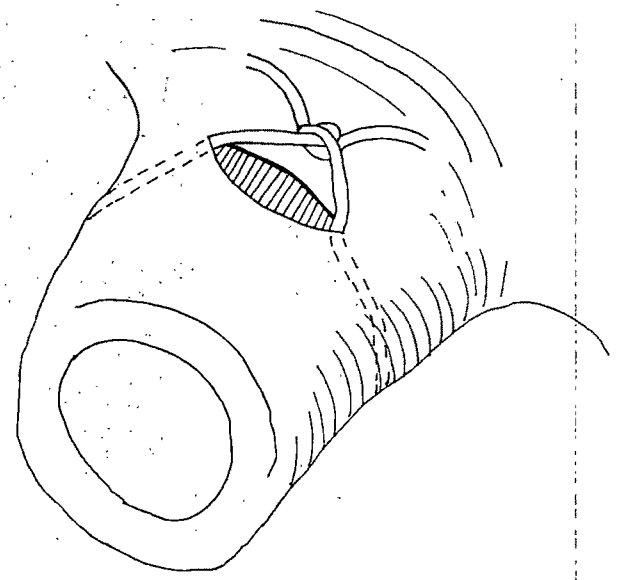


Fig. 3. Knot tied anteriorly.

A group of nine patients had previously undergone 14 unsuccessful cerclage procedures elsewhere (Table I). These same patients were treated subsequently by the authors in 16 pregnancies, and all were carried to 37 weeks or longer with 100% neonatal survival.

There were some patients who had more than one Shirodkar operation, with a maximum of five procedures in one patient. Multiple procedures did not pre-

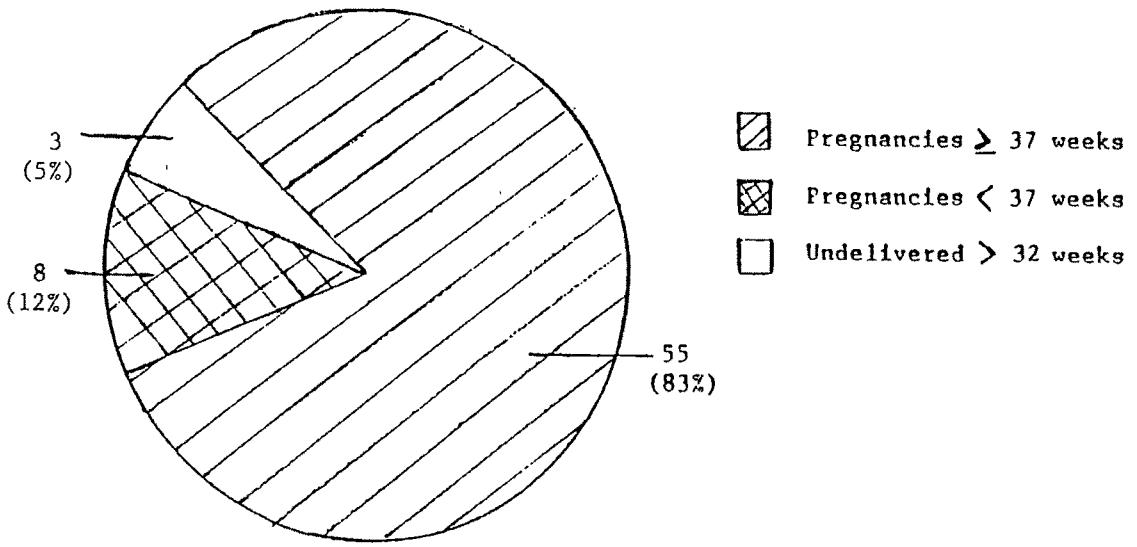


Fig. 4. Outcome of Shirodkar operations.

Table I. Pregnancy outcome in subset of nine women with previous cerclage

Cerclage	*No. of pregnancies*	*No. of term births*
McDonald-unspecified (elsewhere)	10	0
Shirodkar (elsewhere)	4	0
Shirodkar (present series, same patients)	16	16

clude vaginal birth. No cesarean deliveries were performed for indications related to the Shirodkar operation, and an attempt at vaginal delivery was made in every case unless contraindicated for obstetric reasons. The primary cesarean section rate in our series was 23%. In half of the cases a cesarean section was performed for cephalopelvic disproportion. Other indications for primary cesarean section were history of previous extensive cervical laceration with hemorrhage, double footling breech presentation, retinal detachment, severe preeclampsia, prior uterine rupture, and hemorrhage caused by placenta previa. There were no cases of bladder, ureteral, or bowel injury, hemorrhage, or infection. There were no postoperative preterm labors in the first 7 days after the procedure. No patients had uterine rupture or significant cervical laceration by awaiting the onset of labor before removal of the Mersilene band. Three patients did require repair of minor cervical lacerations at suture removal but did not require transfusion since bleeding was minimal. Laceration repair was necessary in two patients in three pregnancies because of a delay in suture removal with precipitate labor and in one patient as a result of a forceps delivery. In two other patients difficulty was encountered in removing the suture but the remaining patients' sutures were easily removed. No patients had infertility or bladder disorders, fistula formation, granuloma formation, or dysmenorrhea after the placement and subsequent removal of the Mersilene band. No long-term adverse effects were noted.

Comment

The pathophysiology of cervical incompetence is not clearly defined. It is probably not one specific abnormality but rather a spectrum of different degrees of anatomic deficiency, including congenital connective tissue defects, multiple small lacerations as a result of trauma, gross cervical tears, and congenital malformations, such as those seen in patients with diethystilbestrol exposure. Varying patterns of uterine contractions as a result of the effects of physical activity and multiple gestation further contribute to cervical incompetence. The final common pathway for cervical incompetence as a result of these factors is painless dilatation of the cervix.

As in all areas of medicine, a correct diagnosis is essential to obtain the optimal therapeutic result. Therefore prepregnancy evaluation and appropriate selection of patients for operation are paramount. Scheduled prophylactic operation in the early second trimester offers a further safeguard because cervical dilatation usually has not yet taken place and the membranes are not exposed. This not only protects the gestational sac, but also simplifies the operative procedure and reduces blood loss. The early second trimester is also preferred because early spontaneous abortion for other causes is no longer a problem. Ultrasonographic verification of fetal viability should be done before the operation is performed.

A recent review of cervical incompetence by Golan

et al.[4] cites fetal survival rates after Shirodkar cerclage of 75% to 85%. In our series 58 of the 66 treated pregnancies (88%) were carried for at least 37 weeks, with 61 surviving infants for an uncorrected perinatal survival rate of 92%.

This is the largest published series of patients treated for incompetent cervix with the Shirodkar operation by a single surgeon. It demonstrates that the operation is effective when used for patients with documented cervical incompetence. There was no morbidity from the procedure, and removal of the Mersilene band as soon as labor began permitted vaginal birth without significantly increased risk to the mother or infant. The Shirodkar operation should be part of resident training and should have a prominent place in the treatment of incompetent cervix. Perhaps a prospective randomized trial that compares the Shirodkar and McDonald procedures should be undertaken to determine the relative merits of these techniques.

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The effect of mode of delivery on the perinatal outcome in fetuses with abdominal wall defects

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A descriptive study of 125 infants with abdominal wall defects was undertaken to determine the effect of mode of delivery on outcome. Fifty-six infants had gastroschisis and 69 had omphalocele. Overall, there were no differences between the omphalocele and the gastroschisis groups in either cesarean section rate (22% vs 26%) or prematurity rate (26% vs 30%). However, the omphalocele group had a significantly higher infant death rate (22% vs 7%, $p < 0.001$), a significantly higher incidence of associated major congenital anomalies (29% vs 5%, $p < 0.001$), and a higher incidence of long-term infant morbidity (14.5% vs 8.9%). Within either group there was no significant difference between vaginal and cesarean delivery regarding either infant mortality, acute or long-term infant outcome, or frequency of associated major anomalies. We conclude that vaginal delivery of infants with abdominal wall defects does not adversely affect infant outcome. (AM J OBSTET GYNECOL 1990;163:833-8.)

Key words: Congenital abdominal wall defects, vaginal delivery, outcome

The incidence of omphalocele is approximately one in 5,800 to one in 5,130 live births, while that of gastroschisis is about one in 10,000 to one in 15,000 live births.[1] Omphalocele represents the persistence of the body stalk in an area normally occupied by the differentiated abdominal wall. A membranous sac usually covers the herniated viscera. Omphalocele is associated with major chromosomal abnormalities. This is reported to be as high as 40% of patients where amniocentesis is performed. In addition, there is an increased incidence of other major structural abnormalities (45%) Gastroschisis involves a defect in the abdominal wall usually to the right of the umbilicus. It has been suggested that this results from abnormal involution of the right umbilical vein that leads to a paraumbilical defect through which small bowel prolapses at approximately 37 days of embryonic life. In gastroschisis, viscera float

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uncovered in the amniotic fluid and lie exposed at birth. The incidence of major chromosomal abnormalities or other structural anomalies is low in this group of fetuses (<5%). Prematurity and low birth weight have been reported to be more common than in omphalocele.[2-4]

There has been an increase in the survival of infants with these defects over the past 10 years. Mortality is related to a number of factors: gestational age at the time of delivery, the condition of the infant before operation, the presence of other anomalies, the size of the lesion, and the type of repair.[5] Now, with the widespread use of obstetric ultrasonography, congenital defects of this sort are being detected in utero with increasing frequency.[6] Since prenatal diagnosis offers the ability to alter the obstetric management, it is important to focus attention on other perinatal factors that may influence neonatal and long-term outcome. Debate has arisen as to the appropriate mode of delivery. Early case reports advocated the use of cesarean section to avoid fetal injury.[7-9] Lenke et al.[10] recommended the use of cesarean section in fetuses with gastroschisis while Nakayama et al.[11] and Kirk and Wah[5] reported that vaginal delivery did not appear to adversely affect fetal outcome for these fetus. In addition, Carpenter et al.[12] reported that vaginal delivery is not contraindicated for the fetus with ventral wall defects.

The purpose of this report is to review our experience of 125 cases of anterior abdominal wall defects and to determine the effect of mode of delivery on neonatal survival and long-term outcome.

Material and methods

The study group consisted of infants with omphalocele or gastroschisis who were referred to the neonatal surgical team at the University of Tennessee, Memphis, between August 1978 and July 1989. Data were collected by chart review performed by the authors. The source of the data included office records of the pediatric surgical team, inpatient and outpatient records of the hospital of origin, records from the neonatal intensive care unit, and, when applicable, autopsy reports. Details of long-term follow-up were obtained from the pediatric clinic that the patients attended and by direct contact with the parents of the infants.

Records were reviewed for birth weight, gestational age, mode of delivery, presence of other major anomalies, size of the defect, and presence of extracorporeal organs, as well as the presence of other neonatal complications. Special attention was given to the ascertainment of trauma to the extracorporeal organs at delivery and, in the case of omphalocele, rupture of the sac. In those cases of omphalocele with a ruptured sac records were carefully reviewed to determine those that appeared to occur at delivery. This was determined principally by observations of the bowel serosa and the presence of thickened matted bowel. It was thought that those infants who had these associated bowel findings most likely sustained rupture of the omphalocele sac before delivery. The changes in the bowel serosa were attributed to exposure of the bowel to the alkaline amniotic fluid, similar to that of gastroschisis.

Gestational age at birth was estimated from the mother's last menstrual period and confirmed where possible by a dating ultrasonogram and Dubowitz examination. Definition of the extent of the ventral wall defect and evidence of any trauma were based on records of the examination by the pediatric surgical team on admission to their unit. The criteria defined by the pediatric surgical team for the diagnosis of omphalocele included those patients with a midline abdominal wall defect with a covering membrane or a remnant of the membrane. Additional criteria included the presence of a dilated umbilical ring containing umbilical vessels passing through the membranous sac without an intervening bridge. The criteria for the diagnosis of gastroschisis were a paraumbilical full-thickness defect of the abdominal wall and a normal umbilical cord insertion independent of the defect with a skin bridge between the ventral defect and the umbilical ring.

The analysis was focused on perinatal outcome, long-term outcome, incidence of surgical complications, and cause of death. The infants were divided into four groups according to mode of delivery for analysis: gastroschisis vaginal group versus gastroschisis cesarean section group and omphalocele vaginal group versus omphalocele cesarean section group.

Analysis of data was performed with χ^2 or Fisher's exact test when appropriate and by Student's t test. A p value of <0.05 was considered significant.

Results

A total of 125 infants was studied: gastroschisis ($n = 56$) and omphalocele $n = 69$). Thirty patients (23.5%) were delivered by cesarean section (21% in omphalocele group and 26% in gastroschisis group). The indications for cesarean section are listed in Table I. One hundred four infants (83%) were delivered at this center. Prenatal diagnosis of the defects was made in 10 (8%) of the cases. All of the infants with ventral wall defects that were diagnosed prenatally were delivered at this center [gastroschisis ($n = 4$) omphalocele ($n = 6$)]. All of the infants with gastroschisis that was diagnosed prenatally survived. Five of six infants with prenatal diagnosis of omphalocele survived. The prematurity rates overall were 26% and 30%, respectively.

Table II summarizes the neonatal and long-term outcome of infants with gastroschisis according to the mode of delivery. There were no significant differences between the vaginal and cesarean section groups re-

garding any of the categories studied. The overall mortality rate in infants with gastroschisis who were delivered by cesarean section was 6.6% and it was 7.3% in the infants who were delivered vaginally. In the gastroschisis group overall, the delivery-operation interval was an average of 6 hours. There was little difference in this interval between the cesarean section group (6.0 hours) and the vaginal delivery group (6.2 hours).

Gastroschisis–vaginal delivery group: Extracorporeal organs other than bowel were present in 16 (28%) of these infants. These included stomach, bladder, fallopian tubes, ovary, omentum, and testis. Extracorporeal liver was not found in any infant within this group. There were no cases of delivery trauma to the extracorporeal organs noted. Intestinal atresia was present in three infants. Overall, 21 infants in this group had primary closure of the defect and 20 required a two-stage repair. Additional bowel surgery was necessary in four infants: bowel resection for volvulus or obstruction ($n=3$), and ileostomy closure $n=1$). It is interesting to note that meconium aspiration syndrome did not occur in any of these neonates. There were three (7.3%) infant deaths in this group: one caused by fungal sepsis at 17 days, one caused by sudden infant death syndrome at 6 weeks, and a late death that was secondary to bowel obstruction and sepsis at 3 years. Long-term follow-up was available for all 41 infants. Three infants suffered from significant morbidity: One infant had long-term nutritional problems and was on a modified diet as a result of short bowel syndrome, one infant had biliary cirrhosis, and the third had failure to thrive.

Gastroschisis–cesarean delivery group. Associated major anomalies were present in two (13%) of these infants: One infant had occipital encephalocele and one infant had trisomy 13 and a large ventricular septal defect. This latter case represented the only infant death among cases of gastroschisis with delivery by cesarean section. Extracorporeal organs present in this group of infants included bladder, stomach, gallbladder, ovaries, and fallopian tubes. None had an extracorporeal liver. Delivery trauma to the extracorporeal organs was not noted in any infant. Associated intestinal atresia was noted in two infants in this group. Primary closure was performed in eight and seven infants required a two-stage repair. Additional bowel surgery (closure of jejunostomy) was necessary in only two infants. All 15 infants had long-term follow-up, and none had any long-term morbidity.

Table III summarizes the clinical characteristics of infants with omphalocele according to the mode of delivery. There were no significant differences for any of the categories studied. The overall mortality rate in infants with omphalocele was 20% in those delivered by cesarean section and 22% in infants delivered vaginally. The causes of infant deaths in the omphalocele group include multiple congenital anomalies ($n=9$), cardiac anomalies ($n=4$), and complications of prematurity ($n=2$).

Table I. Indications for cesarean section

	Omphalocele (n = 15, 22%)	*Gastroschisis (n = 15, 26%)*
Failure to progress–cephalopelvic disproportion	4	3
Elective repeat	4	2
Fetal distress	3	6
Breech	2	2
Other	2*	2†

*Premature rupture of membranes and chorioamnionitis ($n = 1$), maternal genital herpes ($n = 1$).
†Preeclampsia ($n = 2$).

In the omphalocele group the delivery-operation interval was an average of 6.5 hours. There was little difference in the interval between the cesarean section group (6.6 hours) and the vaginal delivery group (5.8 hours).

Omphalocele–vaginal delivery group. There were 16 (30%) infants with major associated anomalies and 22 (41%) with extracorporeal organs other than bowel present. These included stomach, pancreas, spleen, ovary, and fallopian tubes. Eleven infants had extracorporeal liver (partial or complete). There were three (27%) infant deaths among the babies with herniated liver delivered vaginally. Severe cardiac anomalies were the cause of death in two of these infants (Epstein's anomaly, transposition of the great vessels). The third infant died of complications of prematurity. Delivery trauma to the liver was not noted in any of the 11 cases. Eight infants with omphalocele who were delivered vaginally had ruptured sacs. On the basis of examination of the bowel, it was determined that two of the eight must have sustained rupture of the sac before delivery. Among the eight infants with ruptured sacs, there were two infant deaths, both of which were attributed to multiple congenital anomalies. There were no cases of sepsis among these eight infants. Among the infants with omphalocele delivered by the vaginal route, there were three infants with associated intestinal atresia. Thirty-four infants had primary repair and 20 required a two-stage operation. Overall, among the cases with omphalocele and vaginal delivery there were 12 infant deaths, 10 of which were associated with major anomalies and two that were secondary to complications of prematurity. There were 36 surviving babies with isolated omphalocele that underwent vaginal delivery. Thirty-five survived without long-term morbidity, and one died with complications of bowel obstruction at 2 years. Long-term follow-up was available for

Table II. Neonatal and long-term outcome in infants with gastroschisis by mode of delivery

	Vaginal (n = 41)	*Cesarean section (n = 15)*
Gestational age (wk)	37.5 ± 2.6	37 ± 3.1
Birth weight (gm)	2557 ± 564	2575 ± 502
Preterm birth (≤37 wk) (No.)	16 (39%)	4 (27%)
5 min Apgar score (average)	7	8
Cord pH (average)	7.28	7.33
Meconium fluid (No.)	12 (29%)	5 (30%)
Extracorporeal organs (No.)	16 (39%)	8 (53%)
Visceral trauma (No.)	0	0
Major anomalies (No.)	1 (2.4%)	2 (13%)
Infant death (No.)	3 (7.3%)	1 (6.7%)
Follow-up (yr) (mean and range)	3 (0.2-11)	2 (0.5-10)
Morbidity (No.)	5 (12%)	0 (%)

Table III. Neonatal and long-term outcome in infants with omphalocele by mode of delivery

	Vaginal (n = 54)	*Cesarean section (n = 15)*
Gestational age (wk)	38.2 ± 2.2	37.8 ± 2.6
Birth weight (gm)	3020 ± 919	3081 ± 724
Preterm birth (≤37 wk) (No.)	14 (26%)	4 (27%)
5 min Apgar score (average)	8	8
Cord pH (average)	7.26	7.31
Meconium fluid (No.)	5 (9%)	1 (6.5%)
Extracorporeal organs (No.)	22 (41%)	6 (40%)
Visceral trauma (No.)	0	0
Major anomalies (No.)	16 (30%)	4 (27%)
Infant death (No.)	12 (22%)	3 (20%)
Follow-up (yr) (mean and range)	4 (0.2-11)	3 (0.2-11)
Morbidity (No.)	7 (13%)	3 (20%)
Ruptured sac (No.)	8* (15%)	1 (7%)

*Two ruptures were determined to have occurred several days before delivery.

all the infants in the omphalocele–vaginal delivery group. Six infants had significant morbidity: Two had other congenital anomalies (severe scoliosis, ureteral pelvic obstruction), two suffered from complications of preterm birth (chronic respiratory problems), one infant had recurrent urinary tract infections, and the last infant had short bowel syndrome and cirrhosis. This infant had associated intestinal atresia.

Omphalocele–cesarean section group. There were four (27%) infants with major congenital anomalies. Six infants had extracorporeal organs other than bowel. These included stomach, spleen, and bladder. There were five cases with extracorporeal liver. Of these five infants, four survived and were without long-term morbidity. The fifth infant had pentalogy of Cantrell. This infant died after operation. One infant in the omphalocele–cesarean section group had a ruptured sac at delivery. This was reported specifically to have occurred at the time of delivery. The status of the bowel did not indicate prior rupture. This infant survived without long-term morbidity. One infant had an associated intestinal atresia. Primary closure was performed in eight patients in this group and a two-stage repair was necessary in seven. Overall, there were three infant deaths in this group (20%). Two were due to major cardiac anomalies and the third was attributed to extreme prematurity and respiratory complications. Long-term follow-up was available for all 15 patients. Three infants (20%) had long-term complications, all of which were attributed to associated congenital anomalies: atrial septal defect and obstructed ureteropelvic junction, inperforate anus and absent sacrum, and meningomylocele.

Comment

The overall survival rate of 80% in this study is consistent with that reported in other recent studies.[5] The higher mortality rate with omphalocele is also consistent with that of other reports.[3, 12] This increased mortality in the omphalocele group is attributed to the higher rate of associated major anomalies in the omphalocele group as opposed to those infants with gastroschisis (29% vs 5.0%). There was an increased trend toward low birth weight and preterm delivery in the infants with gastroschisis as opposed to those with omphalocele, but the difference did not reach significance. In no case was cesarean section performed solely because of the prenatal diagnosis of abdominal wall defect. This study did not focus on the prenatal diagnosis of these anomalies. Prenatal diagnosis of the defect was made in only 8% of the cases. Although there was no difference in survival between those infants in whom

the defect was diagnosed prenatally and those with diagnosis at delivery, it has been shown in other reports that prenatal diagnosis improves management by allowing maternal transport for labor and delivery at a center specializing in high-risk pregnancy and pediatric intensive care. A key factor in postnatal survival is the clinical condition of the newborn on admission to the pediatric surgical team. Delays in neonatal transport after birth can increase the chances of profound dehydration and risk of sepsis, both causes of poor outcome.[11] In addition, prenatal assessment can determine other associated lethal anomalies and prevent some cesarean deliveries. All the infants were cared for by the same neonatal surgical team. Thus treatment was consistent in all cases.

The most commonly reported postoperative complications in infants with gastroschisis are sepsis, small bowel obstruction, and infarction.[3] It is hypothesized that the combination of uterine contractions and vaginal delivery may lead to vascular compromise and compression of the bowel, thus increasing the chances for these complications. This theory could explain the need for more secondary operations and the greater postoperative complication rate in infants born via the vaginal route.[10] In this study three infants with gastroschisis delivered vaginally required secondary operation for bowel obstruction, but two of the three had associated bowel atresia and required more involved initial surgery. Thus these complications are not due to the delivery process itself but rather are caused by the prenatal state of the organs, such as the presence of secondary bowel atresia. In one other infant massive fungal sepsis resulted in neonatal death at 17 days of age. This infant had an associated major anomaly (bladder extrophy), and sepsis developed late in the postoperative period. Thus it is unlikely that such a complication was associated with the delivery process.

Since one of the major issues in selecting the mode of delivery in these infants is the risk of delivery trauma to the extracorporeal organs, it is important to note that in the 41 infants with gastroschisis delivered vaginally no cases of trauma to the extracorporeal organs at delivery were reported. None of the infants in the gastroschisis group had extracorporeal liver. Thus the effect of mode of delivery in this particular situation cannot be addressed in this study.

Ten of the 12 infant deaths in the omphalocele–vaginal delivery group were due to associated major congenital anomalies and two were due to severe hyaline membrane disease. It is of interest that there were eight cases of ruptured sac in the omphalocele–vaginal delivery group, none of which were complicated by sepsis. Although extracorporeal liver was a relatively common finding in the omphalocele group (22%), there was no improvement in survival rate when the infant was delivered by cesarean section rather than vaginally. This is in contrast to the findings of Sermer et al.,[3] who reported a neonatal death rate of 88% in infants with omphalocele and herniated liver. However, in that report no mention was made as to the presence of other congenital anomalies or perinatal complications that may have contributed to the poor outcome in that group of infants.

There were 36 infants with isolated omphalocele delivered by the vaginal route. There was only one infant death in this group, the cause of which could not have been delivery mode. This further emphasizes the safety of vaginal delivery in this group of patients. In addition, the data support the fact that the majority of the mortality and morbidity in patients with omphalocele can be attributed to other complicating factors, mainly associated congenital anomalies and chromosomal aberrations. Since the primary admission criterion for this study was referral to the pediatric surgical team, it may be postulated that a number of infants were not referred for care because their conditions were critical and that this could be due to visceral trauma sustained at delivery. We feel that this is unlikely for a number of reasons. All infants in this region requiring neonatal intensive care are transferred to this medical center. It is unlikely that visceral trauma would preclude transfer. Facilities for transfer are available, despite the critical nature of the condition of the infants. All infants that present to the neonatal intensive care unit with this sort of lesion would have a pediatric surgical consultation despite their critical condition. Review of the records of the pediatric surgical team would suggest that few cases have been overlooked. We did not focus our analysis on the incidence of stillbirths among fetuses with ventral wall defects nor did we examine the effect of mode of delivery on survival of the previable infant (<24 weeks) with ventral wall defects. We feel there are too many confounding variables to adequately compare these groups.

In summary, our findings suggest that vaginal delivery of infants with abdominal wall defects does not have an adverse effect on neonatal outcome. In addition, long-term infant outcome does not appear to be affected by mode of delivery but rather by other perinatal events. Moreover, the presence of extracorporeal liver in fetuses with omphalocele does not necessarily preclude a vaginal delivery. Until a large, multicenter, prospective randomized study can be accomplished, we believe that cesarean section should be reserved only for obstetric indications in fetuses with abdominal wall defects.

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Perinatal survival with expectant management of midtrimester rupture of membranes

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A retrospective study of 70 patients with preterm premature rupture of membranes before 26 weeks of gestation was performed. The purpose of this study was to examine the perinatal outcome and the potential maternal and neonatal morbidity associated with this obstetric condition. The mean gestational age at diagnosis of rupture of membranes was 23.7 weeks. The latency period ranged from 24 hours to 60 days with the mean being 12 days. There was no correlation between gestational age at rupture of membranes and latency period. Seventy-one infants were delivered. The perinatal survival was 63%. Sixty-eight percent of the survivors had normal neurological and physical development at a 1-year follow-up. Amnionitis developed in 43% of patients. The incidence of respiratory distress syndrome in the neonates was 52%. Betamethasone did not appear to reduce this incidence. The perinatal survival in patients with midtrimester rupture of membranes appears to be improving with the advancements in neonatal care of the extremely premature infant. (AM J OBSTET GYNECOL 1990;163:838-44.)

Key words: Premature rupture of membranes, expectant management, midtrimester, amnionitis, perinatal survival

Premature rupture of membranes (PROM) before the onset of labor occurs in approximately 10% of all pregnancies.[1] The incidence of preterm PROM is about 1%.[2,3] Despite the large amount of data generated concerning the topic of preterm PROM, it remains one of the most controversial topics in obstetrics today.[4] The management of patients with very early preterm PROM in past years usually involved termination of the pregnancy in an attempt to prevent potential maternal morbidity and mortality. In these cases the thought was that the maternal risks greatly outweighed the chances for a normal neonatal outcome. With recent improvements in the neonatal care of the extremely premature infant, there has been an increased interest in the practice of expectant management of patients with preterm PROM.[5]

There have only been four published reports examining the maternal and neonatal outcomes of patients with midtrimester PROM.[6-9] The perinatal survival ranged from 24% in the study by Taylor and Garite[6] in 1984 to 51% in the study by Bengtson and VanMarter[9] in 1988. From these studies and ours, it

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appears that the perinatal survival rates in midtrimester PROM have steadily improved as neonatal care for very-low-birth-weight infants has continued to develop. The contributions of obstetric procedures and regimens are less certain.

In our study, we examined the maternal morbidity of 70 patients with preterm PROM and the subsequent neonatal outcome of 71 delivered infants. All of these patients had pregnancies ranging from a gestational age of 19 weeks to 25 completed weeks. The aim of this study was to evaluate the potential risks and benefits associated with expectant management of patients with very early preterm PROM.

Material and methods

The study group included women who were seen with preterm PROM between Jan. 1, 1984, and Jan. 1, 1988. All of these patients had management at two of the perinatal referral centers in San Francisco—University of California San Francisco Medical Center and Children's Hospital.

All cases of preterm PROM from 19 to 25 weeks were examined. Of 128 cases, 58 were excluded from the study group. The criteria for exclusion were as follows: (1) cervical dilatation >3 cm on admission, (2) diagnosis of an incompetent cervix, (3) cerclage in place, (4) clinical evidence of amnionitis on admission, and (5) desire for elective termination of pregnancy.

Gestational age was determined by last menstrual period and/or ultrasonography, or both. All cases had documented rupture of membranes by Nitrazine testing, ferning, and/or pooling.

All patients without evidence of labor or amnionitis who desired to continue their pregnancies had expectant management consisting of hospitalization with bed rest. On admission all patients had a sterile speculum examination to document rupture of membranes and to obtain cervical cultures. No digital examinations were performed. Patients were monitored with frequent vital signs, complete blood counts, intermittent tokodynamometry, and fetal heart rate evaluation. Antenatal fetal assessment began at 25 weeks and consisted of daily fetal heart rate testing. Before 25 weeks, fetal heart tones were obtained with an electronic fetoscope at least two times each day. Amniotic fluid evaluations were obtained on a weekly basis in the majority of the patients. Patients were taken to labor and delivery for continuous monitoring if they experienced vaginal bleeding, uterine activity, or an abnormal fetal heart rate assessment.

Patients were monitored for the development of amnionitis. A presumptive diagnosis was made in most cases by the presence of two or more of the following criteria: (1) temperature >38° C, (2) persistent leukocytosis (white blood cell count >15,000/ml, (3) uterine tenderness or irritability, and (4) fetal tachycardia. Once the diagnosis of amnionitis was made, antibiotics were begun and labor was induced. All patients were cultured for group B streptococci and were treated if their cultures were found to be positive. Very few patients were given prophylactic antibiotics. In all cases steroids were withheld when there was any suspicion of amnionitis. All patients remained in the hospital until delivery occurred.

Intravenous tocolytics were used at the physician's discretion in patients who were undergoing expectant management and who began experiencing regular uterine contractions. Magnesium sulfate was administered as a 4 gm loading dose and maintained at 2 to 3 gm/hr as a continuous infusion. In a small number of patients terbutaline was begun at 10 μg/min and titrated depending on uterine activity. The intravenous tocolytics were discontinued with any of the following: (1) cessation of uterine activity, (2) evidence of amnionitis, (3) intolerance by patient, (4) cervical dilatation >4 cm. No tocolytics were given prophylactically.

Data regarding the patient's hospital course, as well as the patient's risk factors for PROM, were obtained from the maternal charts. The variables analyzed included gestational age at rupture and delivery, mode of delivery, indications for delivery, neonatal weights, and Apgar scores. These were obtained from both maternal and neonatal charts.

The neonatal hospital courses were carefully reviewed. The diagnosis of the degree of respiratory distress syndrome was made by initial ventilator settings, oxygen requirements, chest x-ray appearance, and overall length of time on the ventilator. The diagnosis of intraventricular hemorrhage was based entirely on ultrasonographic findings. The diagnosis of neonatal sepsis was based on positive blood cultures, neutropenia/leukocytosis, or thrombocytopenia. All of the surviving infants were evaluated with developmental testing until at least 1 year after delivery. Ten of the 45 (22%) surviving infants were followed up for a total of 3 years after delivery.

The frequency of respiratory distress syndrome, infectious morbidity, and the gestational prolongation from steroids and tocolytic therapy were examined. The results were analyzed by a χ^2 test to compare the frequency. The differences were considered to be significant for a p value of <0.05.

Results

The patients included in the study consisted of clinic and private patients, as well as patients transported to either of the referral institutions. The analysis was performed on patients who desired to continue their pregnancies and did not have evidence of labor or amnionitis. The patients' ages ranged from 18 to 38 years

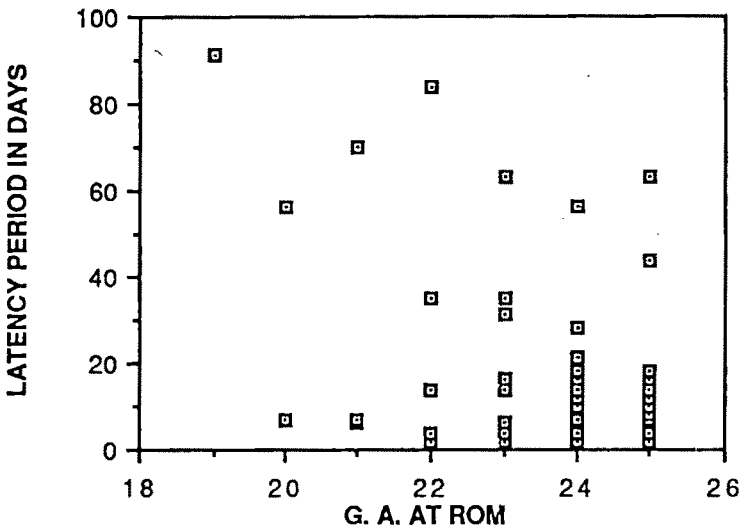


Fig. 1. Correlation between gestational age at rupture of membranes and latency period.

Table I. Indications for delivery

Indication	*No.*	*Vaginal*	*Cesarean section*
Spontaneous labor	34	26	8
Amnionitis with labor	18	13	5
Amnionitis with labor induction	12	10	2
Fetal distress	2	0	2
Elective labor induction	3	2	1
Induction with intrauterine death	2	2	0

Table II. Maternal and neonatal morbidity

	No.	*%*
Maternal condition		
Sepsis	2	2.8
Amnionitis	30	43
Endometritis	12	17
Neonatal condition		
Sepsis	12	17
Intraventricular hemorrhage	8	11
Respiratory distress syndrome	37	52

with the mean being 29 years. Forty-five percent of the patients were primiparous, while 55% were multiparous. A history of previous preterm labor or PROM was identified in 11 patients (15%). Tobacco use was a factor in 20 patients (28%).

The gestational age of rupture of membranes ranged from 19 weeks to 25 completed weeks with the mean being 23.7 weeks. Twenty-nine percent of the patients had occurrence of rupture of membranes before 24 weeks of gestation. Rupture of membranes occurred at a gestational age of <20 weeks in only one patient. The gestational age at delivery ranged from 22 to 34 weeks with the mean being 26.6 weeks. The length of time from rupture of membranes to delivery ranged from 24 hours to 60 days. The mean latency period was 12 days. There was no correlation ($r = 0.24$) between gestational age at rupture of membranes and latency period (Fig. 1). The indications for delivery and the routes of delivery are listed in Table I. Delivery was achieved by the vaginal route in 53 (74%) of the patients. Three of these were vaginal breech deliveries and they were done at gestational ages of <25 weeks. Eleven of the 18 cesarean sections performed were classical. No cesarean sections were performed before a gestational age of 25 weeks.

Of the 70 patients reviewed in this study, 30 (43%) had clinical evidence of amnionitis. Fig. 2 shows the total number of patients within each latent period, as well as the number of patients in whom amnionitis developed with each latent period. This graph shows that 16 of the 28 patients (57%) who were delivered within the first 72 hours had amnionitis. Sixteen (53%) cases of amnionitis occurred within the first 7 days after rupture of membranes. The development of amnionitis after 14 days of rupture of membranes was low (6%). Twelve patients (17%) had a postpartum or postoperative endometritis (Table II). Five of the patients with endometritis had amnionitis before delivery. Eight of the 12 patients (66%) with endometritis had undergone

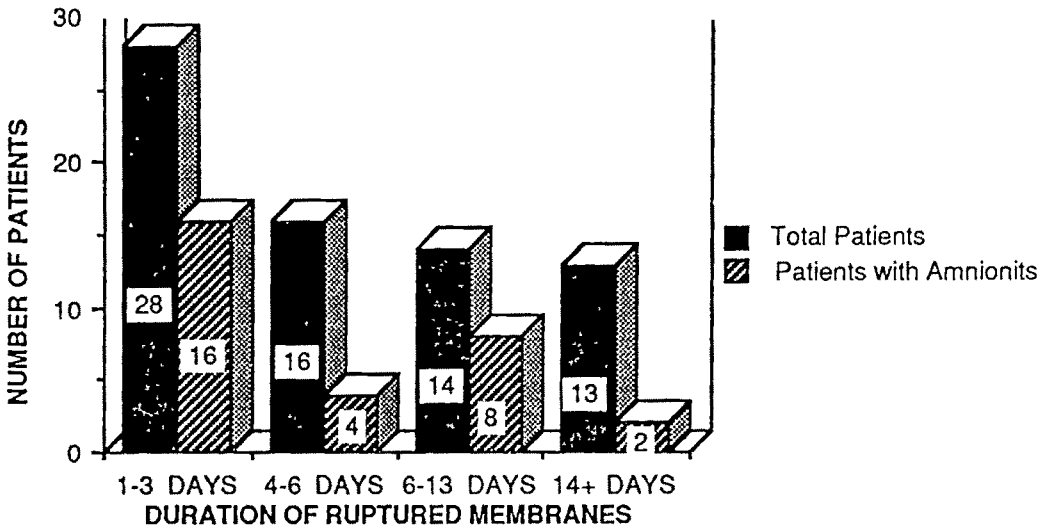


Fig. 2. Latency period of total patient population compared with latency period of those with amnionitis.

Table III. Perinatal outcome

Gestational age at rupture of membranes (wk)	*No.*	*Stillbirth**	*Neonatal death†*	*Perinatal survival‡*	
				No.	*%*
19-21	6	2	0	3	50
21-23	15	5	1	10	64
23-25	25	3	9	21	64
25-26	25	1	5	21	84
TOTAL	71	11	15	45	63

*Causes of stillbirth: abruptio placentae, 5; cord accident, 1; amnionitis, 5; unknown, 4; multiple anomalies, 1.

†Causes of neonatal death: pulmonary hypoplasia, 1; sepsis, 6; respiratory distress syndrome, 9; cardiac anomaly, 1; unknown, 5.

‡Of the 45 survivors, 31 had normal neurologic and physical development at a 1-year follow-up (intact survival-68%)

delivery by cesarean section. The average increase in hospital stays for those patients in whom endometritis developed was 2 days. Two patients had sepsis and one of them went on to experience septic shock, disseminated intravascular coagulopathy, and adult respiratory distress syndrome necessitating care in the intensive care unit. The patient had membrane rupture at 24 weeks with a latency period of 19 days. She had received steroids only (no tocolytics and no antibiotics). Seven (10%) patients required dilatation and curettage for management retained placenta. Three (4%) patients had postpartum hemorrhage; however, only one of them went on to require a transfusion. Two patients required blood transfusions after cesarean section. Perinatal outcome is shown in Table III. Neonatal survival in patients who had rupture of membranes from gestational ages of 19 to 22 weeks was 50%. Survival improved as the gestational age at rupture increased. When rupture occurred at 25 weeks of gestational age, 84% of the infants survived. Overall, from gestational ages of 19 to 25 weeks, 45 of 71 infants survived, resulting in a neonatal survival rate of 63%.

The neonatal mobidity was also evaluated (Table II). Twelve infants (17%) had sepsis. The diagnosis of sepsis was made by either positive blood cultures, elevated or low white blood cell counts, low platlet counts, or clinical symptoms. A grade 2, 3, or 4 intraventricular hemorrhage was apparent in 8 infants (11%). Respiratory distress syndrome was present in some degree in the majority of patients. Moderate to severe respiratory distress syndrome was present in 37 patients (52%). The average length of time on the ventilator was 39.4 days (±7.6 days) in the infants with severe respiratory distress syndrome.

There were 11 stillbirths and 15 neonatal deaths. The total perinatal mortality was 36%. All of the stillborn infants were delivered before 25½ weeks' gestation. The perinatal mortality in relation to gestational age at delivery is shown in Table IV. The average weight for stillbirths was 518 gm (± 180 gm). The majority of still-

Table IV. Distribution of gestational ages at delivery

Gestational age at delivery (wk)	*No.*	*Survival*	*Death*	*Stillbirth*
21	1	0	0	1
22	4	0	0	2
23	4	0	1	3
24	8	1	6	2
25	21	12	6	3
26	7	5	2	0
27	9	10	0	0
28	4	4	0	0
28	13	13	0	0
TOTAL	71	45	15	11

births were thought to be secondary to abruptio placentae ($n = 5$) or were unknown ($n = 4$). Six of the 11 stillbirths were intrapartum deaths at a gestational age of <24 weeks. One of the stillbirths was secondary to a congenital cardiac anomaly incompatible with life. This infant was born at 25½ weeks. There were two other stillbirths that occurred at a gestational age of >25 weeks. One was associated with a massive abruptio placentae. This patient was taken for immediate classic cesarean section. The infant weighed 760 gm and received Apgar scores of 0 and 0. The other one was secondary to a cord prolapse in a 720 gm, 25 ½ weeks' gestation infant. By the time the prolapse was identified, no cardiac activity was noted on ultrasonography. There were 15 neonatal deaths, all of which occurred from 1 hour to 27 days of life. The clinical courses associated with neonatal deaths included sepsis ($n = 6$), respiratory distress syndrome ($n = 9$), asphyxia ($n = 3$), immaturity ($n = 2$), and anomalies ($n = 1$). Autopsies were performed on six of these infants. In only one case was the cause of death thought to be possibly related to hypoplastic lungs. This infant died after only 10 hours of life. Nine infants did not have autopsies, and three of them had clinical courses suggestive of hypoplastic lungs.

Thirty-one of the 45 survivors had normal neurologic and physical development at 1-year follow-up. The intact survival rate after 1 year was 68%. The survivors that did not fall into the "intact" group had a variety of abnormalities such as cerebral palsy ($n = 5$), chronic lung disease ($n = 4$), mental retardation ($n = 3$), blindness ($n = 2$), deafness ($n = 1$), and delayed motor development ($n = 6$).

There were no survivors at gestational ages of <24 weeks at delivery. At 24 weeks there was one survivor who subsequently had chronic lung disease and delayed motor development. There were no neonatal deaths or stillbirths at a gestational age of ≥27 weeks. Table IV depicts the distribution of gestational ages at delivery. The perinatal survival rates for pregnancies in which delivery occurred during the twenty-fifth and twenty sixth weeks were 44% and 71%, respectively. Perinatal survival for deliveries that occured at ≥27 weeks was 100% regardless of gestational age of rupture of membranes.

The management of a number of these pregnancies included measures such as the use of betamethasone and/or tocolytics in an uncontrolled manner at the discretion of the managing physician. Betamethasone was used in 34 patients (48%) (Table V). The average gestational age of the patients who received betamethasone was 25 weeks (±1.9 weeks) as compared with 23.8 weeks (±2.4 weeks) in patients who did not receive betamethasone. This difference in gestational age was not statistically significant. The difference in average birth weights between the two groups was statistically significant (990 ± 200 gm for the betamethasone group compared with 730 ± 110 gm for the nonbetamethasone group). When we reviewed the neonatal outcome, there were no significant differences in the incidences of respiratory distress syndrome, intraventricular hemorrhage, or sepsis between those who received steroids and those who did not. The maternal differences in the incidence of sepsis, amnionitis, and endometritis also were not statistically significant between the two groups.

The average time from rupture of membranes to delivery was 11.1 days (±4.0 days). Twenty-eight patients received intravenous tocolytics (Table VI). The latency period between those who received intravenous tocolytics (12.2 ± 3.8 days) and those who did not (10 ± 3.2 days) was not statistically significant. Again, the majority of patients were delivered of their infants in the first week and this was not affected by the use of tocolytics. It should be emphasized that the use of tocolytics was studied in a noncontrolled manner. Tocolytics were used in those patients having regular uterine contractions. The results revealed that the mean latency period in this group was not significantly less than the mean latency period of the group not having uterine contractions and therefore not receiving tocolytics. These results are not surprising. Neonatal outcome was not affected by the use of tocolytics. The incidences of respiratory distress syndrome, intraventricular hemorrhage, and sepsis were not statistically significant between the group who received tocolytics and the group who did not. Maternal outcome was relatively similar between the tocolytics group and the nontocolytics group. There were no statistically significant differences in the incidences of sepsis, pulmonary edema, endometritis, retained placentas, or postpartum hemorrhages between the two groups.

Comment

This article retrospectively reviews the outcomes of 70 patients with very early PROM. The patient popu-

Table V. Betamethasone and perinatal outcome

	*Betamethasone** (*n* = 34)	*No betamethasone†* (*n* = 37)	*p Value*
Neonatal outcome			
Sepsis	6	6	NS
Severe respiratory distress syndrome	18	19	NS
Intraventricular hemorrhage	5	3	NS
Maternal outcome			
Sepsis	2	0	NS
Amnionitis	6	6	NS
Endometritis	13	17	NS

*Mean gestation, 25 weeks. Mean birth weight, 990 gm.
† Mean gestation, 23.8 weeks. Mean birth weight, 730 gm.

lation within this study does not accurately represent the actual patient population with very early preterm PROM because of the fact that the majority of the patients were perinatal referrals. Management was expectant in all cases. Approximately half of all patients had management with the use of steroids and or tocolytics in an uncontrolled manner.

Because of the enormous advances in neonatal survival at very early gestations, there is a large increase in attention paid to expectant management of preterm PROM. The earliest study on this subject, published by Taylor and Garite[6] in 1984, revealed an overall neonatal survival of 24%. Beydoun and Yasin[7] had a slightly higher gestational age at rupture (19 to 29 weeks) and a higher perinatal survival of 31%. Moretti and Sibai[8] examined patients with PROM between 16 and 26 weeks and also had a perinatal survival of 31%. More recently, Bengtson and VanMarter,[9] in their review of preterm PROM between 19 and 26 weeks, had a survival rate of 51%. The latter authors, as in our study, examined only women with PROM who desired not to terminate their pregnancies and did not have evidence of labor or amnionitis.

In this study our neonatal survival was 66%. The intact neonatal survival was 42%. The intact survival reported from other studies is significantly lower than ours. Our infants underwent follow-up for 1 to 3 years. Previously, the longest reported follow-up of survivors of preterm PROM was < 1 year. The infants who survived with disabilities had a wide range of abnormalities, which included mental retardation, cerebral palsy, blindness, deafness, and motor delays. Some of the developmental problems were mild and some were extremely severe. The majority of severe developmental delays were among the infants in cases of membrane rupture before 24 weeks.

The infants' ultimate survival appeared to depend on the gestational age at delivery and not on the gestational age at rupture of membranes. This finding confirms the findings reported in other studies. Delivery before 24 weeks' gestation produced no survivors. Our apparently high stillbirth rate (15%) is comparable to that of the studies by both Moretti and Sibai[8] and Bengtson and VanMarter[9] which were 13% and 14% respectively. The stillbirth rates in the other two studies by Taylor and Garite[6] and Beydoun and Yasin[7] both exceeded 20%. We feel that our high stillbirth rate is a reflection of our nonaggressive management of pregnancies with a gestational age of <25 weeks.

Table VI. Tocolysis and latency period

	Tocolysis	*No tocolysis*	*p Value*
No.	28	42	<0.001
Mean (days)	12.2	10	NS
>24 hr	7 (25%)	8 (19%)	NS
>48 hr	8 (28%)	4 (33%)	NS
>1 wk	10 (35%)	18 (42%)	NS
Reached 32 wk	3 (10%)	2 (6%)	NS

The maternal findings of a 43% incidence of amnionitis, a 17% incidence of endometritis, and a 2% incidence of sepsis are comparable to those in other studies. In our study, however, there were no serious long-term maternal sequelae. Neonatal complications in this study were frequent. The incidence of severe respiratory distress syndrome was 52%. This was not reduced by either betamethasone or tocolytics. Other authors[9] reported similar findings. The incidence of sepsis was 17%, and again this was not altered by the use of betamethasone or tocolytics. Intraventricular hemorrhage occurred in 11% of the infants born. No improvement in the incidence of intraventricular hemorrhage was noted with either betamethasone or tocolytics. This finding also has been seen by other authors.[10]

Only 1 of 70 infants was thought to have hypoplastic lungs. This is similar to the incidence in the study of Moretti and Sibai,[8] in which only 1 of 118 infants was noted to have hypoplastic lungs. Beydoun and Yasin[7] had no cases of hypoplastic lungs. In contrast, Taylor

and Graite[6] reported that 6 of their 8 neonatal deaths were given a probable diagnosis of hypoplastic lungs. In our study the confirmed diagnosis of hypoplastic lungs in only one infant may be misleading because of the low number of autopsies performed in these patients.

In summary, our results, as well as data from previous studies, provide information concerning the possible risks and benefits of expectant management of very early preterm PROM. This study reveals that the neonatal outcome in patients with midtrimester rupture of membranes is not as dismal as has been portrayed in the past. Our results demonstrate that, as neonatal care has continued to improve, we can counsel our patients with preterm PROM and give a more positive picture of neonatal survival.

The goal of all pregnancies is to have safe delivery of a healthy infant. Expectant management of midtrimester PROM is a reasonable option for patients as long as they are aware of both their potential risks of maternal morbidity and their chances of delivering a normal infant.

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Double-blind comparison of intravaginal prostaglandin E_2 gel and "chip" for preinduction cervical ripening

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The intravaginal application of prostaglandin E_2 for preinduction cervical ripening has proved to be advantageous in the management of patients with an unfavorable cervix. The purpose of this double-blind randomized investigation was to compare the efficacy and safety of two methods of prostaglandin E_2 delivery. Patients who were to have preinduction cervical ripening because of an unfavorable cervix (Bishop score ≤4) were randomly assigned to be given a single dose of prostaglandin E_2 as either 2.5 mg of gel or a 3.0 mg "chip" intravaginally in a placebo-controlled manner. Sixty-nine patients received the active prostaglandin E_2, 34 in the gel group and 35 in the "chip" group. The groups were similar in maternal age, race, parity, gestational age, and initial Bishop score. Both forms of prostaglandin E_2 were easy to administer and helpful in priming an unfavorable cervix. The need for, duration of, and maximum dose of oxytocin were similar in both groups. Cesarean delivery because of failed induction occurred in 5 of 35 (14.3%) patients receiving a "chip" and 4 of 34 (11.8%) receiving the gel. However, patients receiving a "chip" experienced a 20% (7/35) incidence of hyperstimulation, compared with 2.9% (1/36) in those receiving the gel ($p < 0.05$). The only case requiring immediate cesarean delivery because of intractable uterine hyperstimulation received a "chip." We conclude that both methods were effective for cervical ripening, but the lower incidence of uterine hyperstimulation seen with the gel would suggest that it is preferable to the "chip." (AM J OBSTET GYNECOL 1990;163:845-7.)

Key words: Prostaglandin E_2, cervical ripening, induction of labor

Many randomized studies have shown the value and safety of low-dose prostaglandin E_2 (PGE_2) therapy in promoting preinduction cervical ripening and lowering the need for oxytocin during labor.[1-3] The optimal dosage and method of intravaginal delivery remain controversial.[4]

The PGE_2 intravaginal preparation used most commonly is a 1 to 4 mg gel.[4,5] Macer et al.[6] have reported on the use of intravaginal prostaglandin E_2 "chips," prepared by cutting a standard 20 mg PGE_2 suppository into six equal parts. The principal advantage of the "chip" is its widespread availability at labor and delivery units and the lack of compounding requirements in the pharmacy.

The purpose of the current investigation was to compare the effectiveness and side effects of intravaginal PGE_2 "chips" to those of gel in a double-blind randomized manner.

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Material and methods

Approval was granted by our Institutional Review Board. Patients deemed to require induction of labor and having an unfavorable cervix (Bishop score ≤4), intact membranes, and a cephalic presentation were considered candidates for the investigation.[7] After giving informed consent, each subject underwent fetal surveillance with nonstress testing and ultrasonographic assessment of amniotic fluid volume. Additional requirements for enrollment included a reactive nonstress test and normal amount of amniotic fluid (defined by an amniotic fluid index >5).[8]

Each subject received both the gel and "chip" simultaneously, with only one preparation containing PGE_2. Whether PGE_2 was found in the gel or "chip" was determined by our pharmacists using a random numbers table. A single pharmacist prepared the "chips" by cutting a 20 mg suppository (Prostin, The Upjohn Co., Kalamazoo, Mich.) cross-sectionally into six equal parts, each containing 3 to 3.5 mg of PGE_2. An attempt was made to assure that all six "chips" were of uniform size and shape. No attempt was made to compare weights. The same pharmacist prepared the gel by combining methylcellulose with 2.5 mg of PGE_2.[4] It was then placed in a 3 ml syringe, which was frozen until its use.

The portio vaginalis of the cervix was cleansed of

Table I. Comparison of effectiveness of intravaginal PGE_2 "chips" and gel

	Chip (n = 35)	*Gel (n = 34)*	*p Value*
Bishop score change ≥3 after PGE_2	17 (48.6%)	21 (61.8%)	NS
Bishop score ≥5 after PGE_2	23 (65.7%)	27 (64.7%)	NS
Spontaneous labor	12 (34.3%)	12 (35.3%)	NS
Duration of oxytocin (hr)	10.9 ± 7.5	7.4 ± 4.0	NS
Maximum oxytocin (mU/min)	13.6 ± 5.2	12.0 ± 7.2	NS
Duration of labor (hr)	13.9 ± 7.4	11.5 ± 7.8	NS
Cesarean section because of failed induction	5 (14.3%)	4 (11.8%)	NS
Hyperstimulation	7 (20.0%)	1 (2.9%)	0.05

excess mucus with a long cotton applicator. The patient was then given 2.5 ml of the gel (with a 16-gauge intravenous catheter) in the posterior fornix followed by placement of the "chip" inside the vaginal introitus.[4, 6] Uterine activity and the fetal heart rate were monitored continuously for a minimum of 2 hours while the patient remained in a semirecumbent position. If contractions were less frequent than two every 10 minutes and the fetal heart rate was normal, the patient was allowed to ambulate. Those patients who had signs of uterine hyperstimulation (previously unrecorded uterine contractions leading to decelerations of the fetal heart rate or sustained, excessive discomfort) were treated with intravenous or subcutaneous doses of 250 mcg of terbutaline.

Subjects were reexamined in approximately 12 hours (usually at 7 AM) and a post-PGE_2 Bishop score was assigned. If the patient was not already in active labor (regular uterine contractions with a cervical dilatation ≥3), we began intravenous oxytocin for augmentation or induction of labor. Guidelines recommended by the American College of Obstetricians and Gynecologists[9] were followed. An amniotomy was customarily performed once the cervix dilated to 3 cm.

The duration of labor was defined as the time from onset of regular uterine contractions every 3 minutes, either spontaneously or oxytocin-induced, until vaginal delivery. Cesarean delivery was considered in cases of failed induction if the cervix did not dilate beyond 3 cm despite adequate labor for at least 8 hours. Outcome comparisons included the following parameters: Bishop scoring before and after prostaglandin administration, percentage of patients entering spontaneous labor, duration of labor, maximum rate of oxytocin infusion, incidence of uterine hyperstimulation, route of delivery, Apgar scores, and umbilical cord gas determination.

After all the data were recorded, the code was broken for comparative purposes. Proportional data were analyzed by Fisher's exact test. Averaged data were reported as mean ± 1 SD and analyzed with a two-tailed Student t test. A p value of <0.05 was considered statistically significant.

Results

Sixty-nine patients agreed to enrollment and were randomly assigned to receive active PGE_2 in either the "chip" (35 patients) or the gel (34 patients). The groups were statistically similar with respect to maternal age (23.3 ± 5.2 vs 23.3 ± 3.6 years), parity (1.0 ± 1.4 vs 0.57 ± 0.07), and pre-PGE_2 Bishop score (3.1 ± 1.1 vs 3.3 ± 0.8). Gestational age, race, and indications for induction (postdates, hypertension, suspected intrauterine growth retardation, and diabetes) were also similar.

Both groups of patients responded favorably to the administration of prostaglandin. There were no statistically significant differences between the groups in post-PGE_2 Bishop score change, successful induction of labor, and cesarean delivery because of failed induction. The need for, duration of, and maximum dose of oxytocin also were similar between the treatment groups. Approximately half of the patients in each group who required oxytocin received it only for augmentation of spontaneous labor. One patient receiving the "chip" experienced mild nausea with vomiting. Fever and diarrhea were not seen in any study patient.

Table I compares the effects of the two types of administration. A total of eight cases of uterine hyperstimulation were present. The rate of hyperstimulation in the gel group was 2.9% (one case) compared with 20.0% (seven cases) in the "chip" group. This difference was statistically significant ($p < 0.05$). This condition began within the first hour after instillation and appeared as very frequent (more than 5 in 10 minutes) and often strong contractions. Administration of terbutaline was successful in normalizing uterine contractions in 87.5% (seven of eight cases). The normalization usually began withinm 5 minutes after tocolytic therapy, regardless of hyperstimulation pattern. The one case in which contractions persisted despite multiple doses of terbutaline required eventual cesarean delivery. The infant did well.

Three cases in the "chip" group and one in the gel group required cesarean delivery because of fetal distress. All occurred after several hours of labor and appeared unrelated to PGE_2 administration. The out-

comes of all infants in this study were favorable. When compared with those patients recieving an active "chip," patients receiving gel were delivered of infants that were similar in birth weights (3450 ± 670 vs 3312 ± 554 gm). Differences between the "chip" and gel groups also were not statistically significant with respect to the frequency of 1-minute Apgar scores <7 (n = 3 or 8.6% vs n = 3 or 8.8%) and 5-minute Apgar scores <7 (n = 2 or 5.7% vs 0). No infant in either group had an umbilical artery pH < 7.20.

Comment

The optimal method for preinduction cervical ripening should be safe, efficacious, noninvasive, and free of troublesome side effects. PGE_2 gel has been used successfully by many investigators and appears to be the drug of choice for this clinical situation. This agent is thought to split, separate, and dissolve tightly woven bundles of collagen fibers in the cervix. The use of PGE_2 gel in some institutions has been hampered by the reluctance of pharmacists to compound a Food and Drug Administration nonapproved drug into a vehicle that is applied intravaginally. PGE_2 "chips" obviate the need for pharmacy involvement.

The present study represents what we believe to be the first comparison between these two methods of PGE_2 administration. The two groups of patients in this double-blind study were similar with respect to their demographics and their indication for delivery, permitting an accurate comparison of the two groups. Both methods of prostaglandin administration appeared to yield equivalent changes in the Bishop score and were successful in promoting cervical ripening. The overall incidence of vaginal delivery reported here (86% to 88%) compares favorably with other reports.[4]

Although the primary aim of low-dose PGE_2 therapy is cervical ripening, uterine contractions occur coincidentally but are usually "silent" or mild. Of concern is excessive and undesired stimulation, which we defined as contractions becoming so frequent as to cause fetal or maternal distress and warrant tocolytic therapy. The incidence of uterine hyperstimulation in the present investigation varied from 2.9% in the gel group to 20% in the "chip" group. The incidence of hyperstimulation in the gel group was similar to our prior experience and to reports in the world literature. Hyperstimulation usually occurred within several minutes after PGE_2 administration, since absorption velocities are rapid.[10] It was rapidly reversed with subcutaneous terbutaline therapy.

We were surprised to find such a high frequency of uterine hyperstimulation in the "chip" group. The reasons for this unanticipated finding are speculative but may relate to a slightly higher dose of PGE_2 in the "chip" or difficulties in assuring that all "chips" were of equal size. If we assume that the "chips" were of equal size and shape, the most likely explanations for these results are unequal distribution of the drug within the suppository and different rates of absorption between "chips." Because of the rate of hyperstimulation, we decided to discontinue the study, since we saw no distinct advantage of the "chip" over the gel.

On the basis of these observations, we conclude that the use of PGE_2 gel is preferable to "chips" of PGE_2 for the promotion of cervical ripening in patients with an obstetric indication for delivery and an unfavorable cervix. Other adverse effects after PGE_2 administration, during labor and immediately postnatally, were not found regardless of the presence or absence of uterine hyperstimulation. Close monitoring remains necessary so that tocolytic therapy can be instituted early and rapidly reverse any excessive PGE_2-induced contractions.

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Vaginal breech delivery: A five-year prospective evaluation of a protocol using computed tomographic pelvimetry

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In 1983 a protocol was established at our institution that used computed tomographic pelvimetry to evaluate patients presenting with a singleton term frank breech fetus for an attempt at vaginal delivery. The criteria for a trial of labor were singleton fetus, term gestation (37 to 42 weeks' gestation from the first day of the last menstrual period), frank breech presentation, estimated fetal weight 2000 to 4000 gm, non-extended fetal head, and adequate computed tomographic pelvimetry. Two digital radiographs and a tomographic cross-section were taken of each patient, i.e., an anteroposterior view, a lateral view, and an axial section through the femoral head at the level of the fovea capitalis. Adequate pelvimetry was defined as: anteroposterior diameter of the inlet ≥10.0 cm, transverse diameter of the inlet ≥11.5 cm, transverse (interspinous) diameter of the midpelvis ≥9.5 cm, and posterior sagittal diameter of the midpelvis ≥4.0 cm. The purpose of this prospective analysis was to determine the obstetric and perinatal outcome of those breech fetuses that were evaluated with these criteria during the study period of January 1984 through July 1989. During this period the incidence of breech deliveries at our institution was 2.71% (394/14,542). Of these 394 breech deliveries, 122 patients underwent computed tomographic pelvimetry. Eighty-five patients had adequate pelvimetry, fulfilling the protocol criteria, and formed the study group. Eighty-one percent (69/85) of the study group had successful vaginal deliveries (group 1). Nineteen percent (16/85) required cesarean delivery after a trial of labor (group 2) (10 with fetal distress and six with arrested labor disorders). Of the 37 patients who had inadequate computed tomographic pelvimetry and underwent cesarean delivery without a trial of labor (group 3), 54% (20/37) had an extended fetal head, 21.6% (8/37) had an inadequate transverse diameter of the inlet, 13.5% (5/37) had an inadequate midpelvic posterior sagittal measurement, and 10.8% (4/37) had an inadequate interspinous diameter. Perinatal outcome including Apgar scores, cord gases, length of hospital stay, neonatal complications, was evaluated. No difference in infant complications was noted between the group delivered vaginally and the groups delivered abdominally. The only maternal complications in our study group were chorioamnionitis, endomyometritis, and postpartum anemia. There were no significant differences in the incidence of chorioamnionitis among the three groups of patients. There was a higher incidence of endomyometritis in group 2 ($p < 0.01$), than in groups 1 and 3. Interestingly, group 3 experienced a significantly greater incidence of postpartum anemia ($p < 0.01$) when compared with groups 1 and 2. The total radiation exposure to the fetus from computed tomographic pelvimetry is estimated to be approximately 82 mrad, whereas with conventional x-ray pelvimetry the infant may be exposed to as much as 500 to 1100 mrad. Our findings document that computed tomographic pelvimetry is an effective tool in the assessment for vaginal delivery of the singleton term frank breech fetus. (Am J Obstet Gynecol 1990;163:848-55.)

Key words: Breech delivery, pelvimetry, computed tomography

Before the late 1950s, the vaginal route was the method of delivery for breech fetuses. In 1956, Hall and Kohl[1] first suggested routine cesarean delivery in an effort to reduce the excessive perinatal morbidity and mortality then associated with vaginal breech deliveries. Shortly thereafter, Wright[2] reaffirmed this recommendation. Since that time, the cesarean section rate for breech delivery has risen from 4% to 10% up to 80% to 90%.[3] This increase in abdominal deliveries, however, has been associated with an increased risk of maternal morbidity. Furthermore, the increased rate of cesarean deliveries has not resulted in a concomitant improvement in neonatal and infant outcome.[4] Over the past 20 years, much attention has been focused on the reevaluation of vaginal delivery of the breech fetus.

Numerous investigations have demonstrated the

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safety of vaginal delivery for selected term frank breech infants.[5-7] Huchcroft et al.,[8] in a long term follow-up investigation, compared early outcome parameters with behavioral and health criteria at age 2½ and 8½ years. No differences existed between breech babies delivered vaginally and those who were products of cesarean sections. Several investigators[9, 10] have demonstrated that vaginal delivery of selected term breech infants, using strict management protocols including conventional x-ray pelvimetry, significantly improved perinatal outcome when compared with that of breech deliveries managed without benefit of similar protocols. Accordingly, most specialists in maternal-fetal medicine now advocate a trial of labor for the selected breech fetus.[11]

Practical application of conventional x-ray pelvimetry, however, is limited by the relatively high radiation dose to which the infant is exposed, as well as wide variation in film quality. In 1985, Gimovsky et al.[12] suggested that measurements made by computed tomographic pelvimetry might be more precise and reproducible than those obtained by conventional x-ray film.

In 1986, Kopelman et al.[13] published the results of a protocol using computed tomographic pelvimetry to assess the term breech fetus for vaginal delivery. Results of this preliminary investigation demonstrated the utility and safety of such a protocol. The purpose of this prospective investigation is to report our 5-year experience with computed tomographic pelvimetry in the management of the term frank breech fetus.

Material and methods

This investigation was performed at Madigan Army Medical Center during the period Jan. 1, 1984, through July 31, 1989. All singleton term (37 to 42 weeks' gestation) frank breech fetuses were eligible for enrollment. Gestational age was determined by a minimum of two of the following criteria: first day of last menstrual period, Doptone with audible heart rate by 12 weeks' estimated gestational age, fetoscopic confirmation of fetal heart rate by 20 weeks' estimated gestational age, fundal height appropriate for gestational age during second trimester, or ultrasonography performed during first or second trimester. Informed written consent for diagnostic studies was obtained from patients in accordance with criteria established by our institutional review committee. All obstetric patients who were identified as having fetuses in breech presentation underwent ultrasonographic examination to assess estimated fetal weight and exclude the presence of multiple gestation, placenta previa, and/or congenital anomalies. At 37 weeks' estimated gestational age or beyond, patients whose ultrasonographic estimated fetal weights[14] were between 2000 and 4000 gm were scheduled for a nonstress test (NST). If the NST was reactive, an external cephalic version was attempted. If the version was unsuccessful, the patient was discharged after a repeat reactive NST with instructions to return for weekly NSTs and follow-up visits in our routine obstetrics clinic. On presentation in labor, confirmation of frank breech presentation was made via ultrasonography, and a repeat ultrasonographic estimate of fetal weight[14] was obtained. If the estimated fetal weight met our criteria, the patient was transported, after documentation of a reassuring external fetal heart rate tracing, to the radiology department for computed tomographic pelvimetry. Interpretation of the computed tomographic pelvimetry was performed by an experienced member of the obstetrics house staff.

The computed tomographic scanner used during the study period was a General Electric model 8800 (General Electric Medical Systems, Milwaukee). As in the preliminary study by Kopelman et al.,[13] the method for pelvimetric measurements was that originally described by Federle et al.[15] Throughout the computed tomographic study, the patient was maintained in a dorsal supine position. Two digital radiographs and a cross-sectional tomograph were taken: an anteroposterior view, a lateral view, and an axial section through the femoral head at the level of the fovea capitalis. The anteroposterior view served as a fetogram (Fig. 1), allowing determination of the attitude of the fetal head. The transverse diameter of the pelvic inlet was measured from this film. The level of the fovea capitalis was obtained and used to determine the level of the axial section. The transverse diameter of the midpelvis was then measured from this axial section (Fig. 2). The lateral view was used to measure the anteroposterior diameter of the pelvic inlet (Fig. 3) and the posterior sagittal diameter of the midpelvis (Fig. 4). The lateral radiograph also permitted visualization of the contour of the sacrum. On completion of the pelvimetry study patients were considered eligible for vaginal delivery if all the following criteria were fulfilled: frank breech presentation, estimated fetal weight 2000 to 4000 gm, nonextended fetal head, anteroposterior diameter of inlet $\geq$10.0 cm, transverse diameter of the inlet $\geq$11.5 cm, transverse (interspinous) diameter of the midpelvis $\geq$9.5 cm, and a posterior sagittal diameter of the midpelvis $\geq$4.0 cm. These measurements represent a composite of critical values described by Benson et al.[6] and Collea et al.[7]

The radiation dose absorbed by the fetus from each of the two digital radiographs is approximately 22 mrad. The dose from the axial section is approximately 38 mrad. This results in an estimated radiation exposure of 82 mrad.[17]

The Statview II computer software statistical package (Abacus Concepts, Inc., Berkeley, Calif.) was used for analysis of data. A χ^2 test was used to compare the

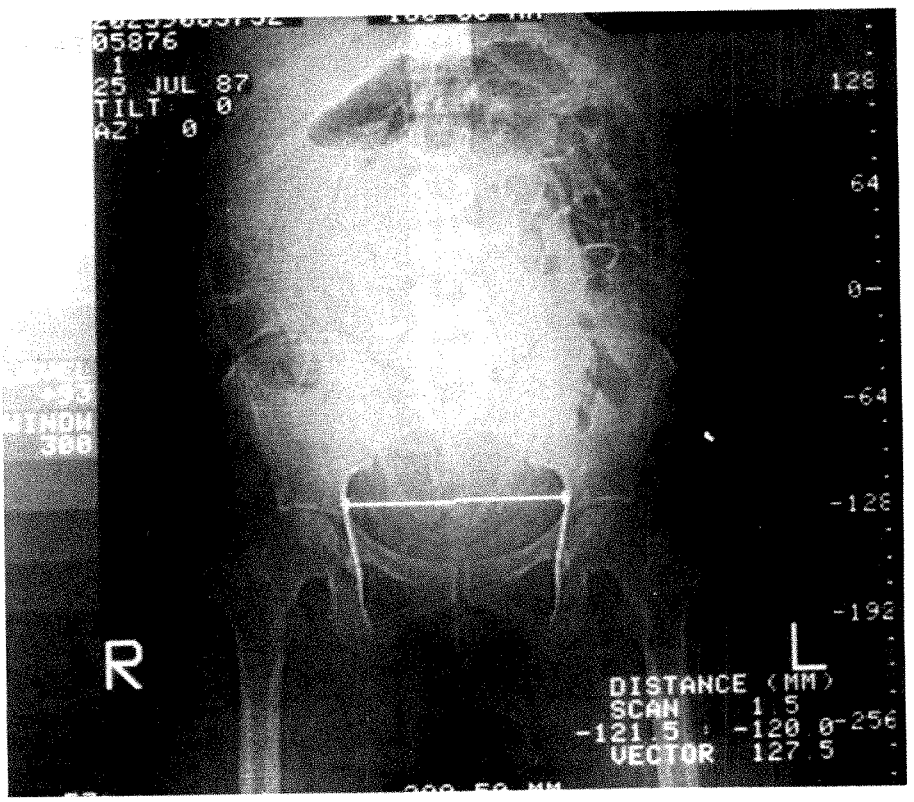


Fig. 1. Anteroposterior digital radiograph of the pelvis as a fetogram, allowing determination of the attitude of the fetal head and measurement of transverse diameter of the pelvic inlet.

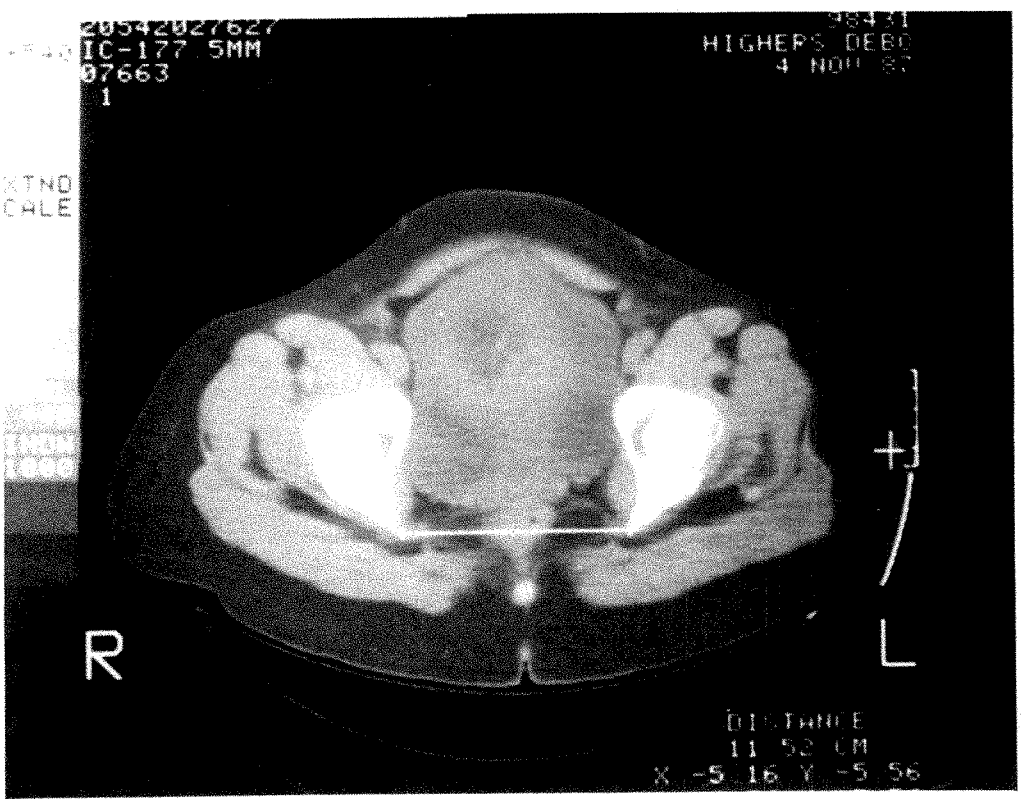


Fig. 2. Axial computed tomographic section taken at the level of fovea capitalis, which permits measurement of transverse diameter of the midpelvis.



Fig. 3. The lateral view is used to measure both anteroposterior diameter of the pelvic inlet (Fig. 3) and posterior sagittal diameter of the midpelvis (Fig. 4).

difference in maternal morbidity between the patients delivered vaginally and those delivered abdominally. The Kruskal-Wallis test was used to analyze Apgar scores. The Scheffé F test was used to evaluate arterial and venous umbilical cord pH differences between breech fetuses delivered vaginally and those delivered abdominally. We considered a probability value <0.05 to be statistically significant.

Results

During the study period the incidence of breech delivery was 2.7% (394 of 14,542 deliveries). Of these 394 breech deliveries, 159 (40.4%) fulfilled criteria for gestational age, ultrasonographic fetal weight, and frank breech presentation, thus making them eligible for computed tomographic pelvimetry. Computed tomographic pelvimetry was obtained on 122 (77%) of the 159 eligible frank breech fetuses. The remaining 37 patients could not undergo the procedure because of advanced cervical dilation or rapidly progressing labor at the time of presentation. Eighty-five of the 122 patients who underwent computed tomographic pelvimetry were determined to have adequate pelvimetric measurements. These women formed a study population consisting of two groups. Group 1 consisted of those women who were successfully delivered vaginally. Group 2 consisted of those women requiring cesarean delivery after an unsuccessful trial of labor. The remaining 37 patients (group 3) had inadequate pelvimetry measurements and required cesarean delivery. Reasons for inadequate pelvimetry were extended fetal head, 54% (20/37); inadequate transverse diameter of the inlet, 21.6% (8/37); inadequate posterior sagittal diameter of the midpelvis, 13.5% (5/37); and inadequate interspinous diameter, 10.8% (4/37). Fig. 5 summarizes the clinical outcome of all patients presenting in labor with breech fetuses.

Of the 85 patients with adequate pelvimetry, 81.2% (69/85) achieved vaginal deliveries (group 1) and 18.8% (16/85) had cesarean deliveries after a trial of labor (group 2). Obstetric indications for abdominal delivery included 10 for fetal distress and six for arrested labor disorders. The diagnostic criteria of Friedman and Sachtleben[18] for arrested labor disorders were strictly followed. Table I depicts the characteristics of those patients who had adequate pelvimetric values but ultimately required cesarean delivery because of arrested labor.

For purposes of evaluating maternal morbidity and neonatal outcome, the patient-infant pairs were divided into the same groups mentioned above. Table II displays the median Apgar scores, as well as the mean

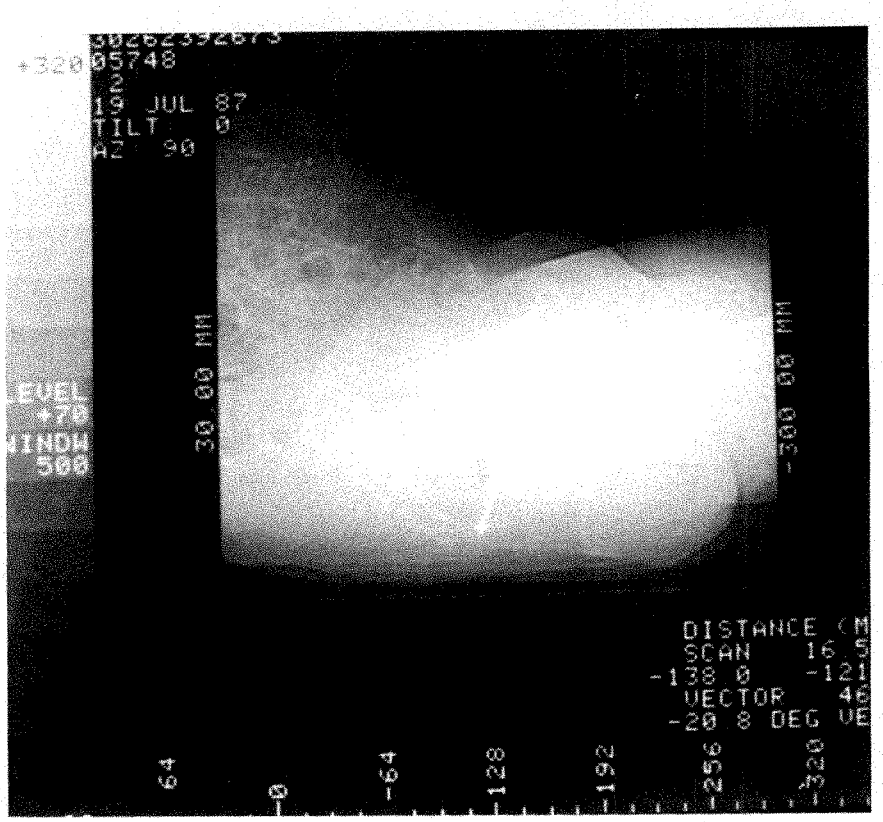


Fig. 4. The lateral view allows not only measurement of the posterior sagittal diameter of the midpelvis but visualization of the contours of the sacrum as well.

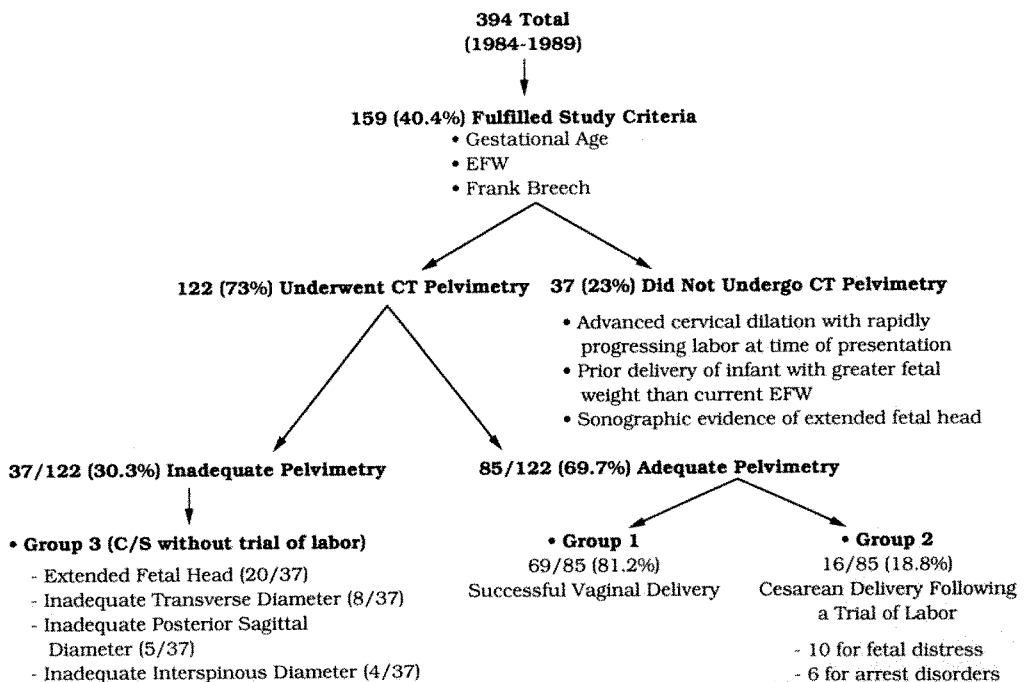


Fig. 5. Clinical outcome of all patients presenting in labor with breech fetuses.

Table I. Characteristics of patients with adequate computerized tomographic pelvimetry but ultimately requiring cesarean delivery for arrest of labor

Age (yr)	*G/P*	*EFW (gm)*	*Labor anesthesia/analgesia*	*CVX*	*Duration of labor arrest (hr)*	*BW (gm)*
18	3/1	2824	Narcotic	100%/5	2	3150
19	2/1	3800	Epidural	100%/5	2	3720
24	2/1	3550	Epidural	100%/8	2	3327
26	1/0	3350	Epidural	100%/6	2	3340
27	1/0	3775	Epidural	100%/5	2	3350
19	2/1	3630	Narcotic	100%/6	2	3950

G/P, Gravidity/parity; *EFW*, estimated fetal weight; *CVX*, cervical examination at time of diagnosis of arrest; *BW*, birth weight.

Table II. Parameters of neonatal outcome in each group

	Group 1 (n = 69)	*Group 2 (n = 16)*	*Group 3 (n = 37)*	*Significance*
Apgar score (median)				
1 min	7	8	8	NS*
5 min	9	9	9	NS*
Umbilical cord pH (mean)				
Artery	7.18	7.25	7.26	$p < 0.05$†
Vein	7.29	7.31	7.30	NS†

*Kruskal-Wallis test.

†Scheffé F test.

Table III. Maternal complications in each group

	Group 1 (n = 69)		*Group 2 (n = 16)*		*Group 3* (n = 37)*		χ^2: *Groups 1 and 2*	χ^2: *Groups 1 and 3*
	No.	*%*	*No.*	*%*	*No.*	*%*		
Chorioamnionitis	4	5.8	5	31.2	0		NS	NS
Endomyometritis	1	1.5	7	43.8	1	2.7	$p < 0.01$	NS
Postpartum anemia	6	8.7	1	6.3	1	6.3	NS	$p < 0.01$

*Additional complications included one spinal headache and one wound separation.

arterial and venous cord pH values. Table III demonstrates the distribution of maternal complications. Chorioamnionitis was defined as the presence during labor of a maternal temperature >100.4°F, with or without associated fetal tachycardia and or uterine tenderness. Endomyometritis was defined as maternal temperature >100.4°F at any time after vaginal delivery or after 24 hours in cesarean deliveries. In both instances absence of other identifiable sources of infection was required to make the diagnosis.

Comment

Computed tomographic pelvimetry has been reported to be as reliable as conventional x-ray pelvimetry in predicting the likelihood of successful vaginal delivery.[12, 13] Moreover, computed tomographic pelvimetry has several advantages when compared with conventional x-ray pelvimetry. First, because of differences in technique and improved film quality, pelvimetric measurements are more easily interpreted and readily standardized with computed tomographic technology. With x-ray pelvimetry, variations in the skill and level of experience of the x-ray technician can result in errors, requiring repeat studies. This can be avoided with computed tomographic pelvimetry. Computed tomographic pelvimetry exposes the patient and fetus to a significantly lower radiation dose. The dose absorbed by the fetus from each of the two digital radiographs is approximately 22 mrad. The dose from the axial section is approximately 38 mrad. Computed tomographic pelvimetry results in a total fetal dose of approximately 82 mrad.[17] In contrast, conventional x-ray

pelvimetry exposes the infant to between 500 and 1100 mrad.[19] Finally, computed tomographic pelvimetry requires neither postural change nor awkward ruler placement and is much more comfortable for the patient than is conventional x-ray pelvimetry.

In 1986, Kopelman et al.,[13] using our current protocol, evaluated 32 singleton term breech pregnancies for trial of labor. Of the 17 patients who fulfilled the criteria for attempted vaginal delivery, 82.4% (14/17) were delivered vaginally. These original results, as well as our current findings, are similar to or better than those obtained with conventional x-ray pelvimetry. Collea et al.[7] found that 82% of their study group who met the criteria for trial of labor went on to deliver vaginally. Gimovsky et al.[12] found a 66% vaginal delivery rate among patients approved for trial of labor. All three groups of investigators[7, 12, 13] found no increase in perinatal morbidity or mortality for vaginal delivery of the breech fetus when careful selection criteria were used.

In this study, which expands the original study group used by Kopelman et al., 81.2% (69/85) of our study group with adequate computed tomographic pelvimetry were delivered vaginally. This is the largest prospective investigation to date assessing computed tomographic pelvimetry in the evaluation of the selected term frank breech fetus. Our success rate for vaginal breech delivery (81.2%) was accomplished with no significant maternal or perinatal complications. Our results compare favorably to the success rate previously reported from our institution with conventional x-ray techniques. Between 1980 and 1984, Watson and Benson[5] retrospectively evaluated 254 term breech deliveries at Madigan Army Medical Center. In their study 75.8% (69/91) of patients with an estimated fetal weight <4000 gm and adequate or borderline adequate x-ray pelvimetry were delivered vaginally.

There were no clinically significant differences in perinatal outcomes among the three groups of patients when compared for Apgar scores, venous cord gases, duration of hospitalization, or discharge diagnoses recorded in the infants' charts. The statistically lower mean umbilical cord artery pH in the vaginally delivered group is not unexpected. The mean umbilical cord venous pH is well within the accepted normal range. Although our data document a lower umbilical cord artery pH, evidence already exists in the literature that our excellent median 5-minute Apgar score is predictive of no long-term ill effects.[8] Thus, despite the findings of a statistically lower mean umbilical cord artery pH in breech fetuses delivered vaginally, it is unlikely to be of any clinical significance and probably represents acute cord compression during the second stage of labor. Since umbilical cord venous pH is a good indirect measurement of placental function, our data suggest that there was no difference in placental function between those breech infants delivered vaginally and those delivered abdominally. Thus, our data support the findings of other investigators that there was no difference in fetal outcome between infants delivered vaginally and those delivered abdominally.

As expected, uterine infection after cesarean delivery was more common among those patients who labored and ultimately required abdominal delivery ($p < 0.01$) than among those patients who were delivered vaginally. Of note is the significantly higher incidence of postpartum anemia ($p < 0.01$) in the group who, because of inadequate pelvimetry, underwent cesarean delivery without experiencing a lengthy labor. This finding is most likely attributable to an unlabored lower uterine segment and resultant greater intraoperative blood loss.

Our overall incidence of 2.7% breech deliveries is lower than the usually reported incidence of 3% to 4% and is directly attributable to our active external cephalic version protocol for all term breech presentations. In 1987, Robertson et al.[20] reported a success rate of 67% for external cephalic version at our institution.

In conclusion, this series is the largest investigation to date that evaluates the outcomes of selected vaginal term frank breech deliveries by means of computed tomographic pelvimetry. The 81.2% rate of successful vaginal breech delivery with our protocol is noteworthy because there were no significant increases in maternal or perinatal complications. This protocol involves very little risk to the fetus and avoids the maternal morbidity associated with unnecessary cesarean delivery. Our findings document that computed tomographic pelvimetry is an effective tool in the assessment for vaginal delivery of the singleton term frank breech fetus.

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The incidence of significant fetomaternal hemorrhage in patients undergoing cesarean section

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To determine the incidence of fetomaternal hemorrhage in patients undergoing cesarean section, Kleihauer-Betke tests were performed in the immediate postoperative period on 199 parturients. Some degree of hemorrhage was detected in 18.5% of patients, with 2.5% demonstrating >30 ml of fetal blood. Comparison of groups on the basis of indication for cesarean delivery revealed no difference in rates of fetal hemorrhage. Because patients with >30 ml of fetal blood would not be adequately protected from Rh sensitization by the standard 300 μg dose of Rh immune globulin, we recommend screening all Rh-negative patients undergoing cesarean section for the presence of significant fetomaternal hemorrhage. (AM J OBSTET GYNECOL 1990;163:855-8.)

Key words: Fetomaternal hemorrhage, Rh sensitization

The widespread use of postpartum and antepartum Rh immune globulin has significantly reduced the incidence of hemolytic disease of the newborn as a result of maternal Rh isoimmunization. However, there remains a small number of patients (0.2% to 1%) who become sensitized at the time of delivery,[1] perhaps as a result of significant fetomaternal hemorrhage occurring at that time. Because the standard dose of Rh immune globulin (300 μg) covers up to 30 ml of fetal hemorrhage,[2] any degree of fetomaternal hemorrhage above this threshold could result in sensitization.

Previous studies have suggested several different clinical factors that may increase the risk of significant fetomaternal hemorrhage including forceps delivery, manual removal of the placenta, multiple gestation, fetal distress, and cesarean section.[3-7] However, there is no consensus as to which, if any, of these factors can identify a group of patients who should be tested at the time of delivery to quantify the degree of fetomaternal hemorrhage.[8-9]

The purpose of this study was to determine the incidence of significant fetomaternal hemorrhage in patients undergoing cesarean delivery at our institution to decide whether routine quantification of fetomaternal hemorrhage was justified to identify patients who require extra Rh immune globulin.

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6/6/22597

Table I. Clinical characteristics of patients with significant fetomaternal hemorrhage (>30 ml)

Patient	*Gravidity*	*Parity*	*Gestational age (wk)*	*Amount of fetomaternal hemorrhage*	*Indication for cesarean section*
J. B.	1	0	36	43.0	Breech, bicornuate uterus
D. F.	3	2	41	37.7	Fetal distress, abruptio placentae?
M. M.	1	0	28	31.2	Fetal distress, eclampsia
A. G.	6	1	38	45.7	Elective repeat—no complications
B. B.	3	1	38	48.2	Fetal distress

Material and methods

The E. H. Crump Women's Hospital is a tertiary care center affiliated with the University of Tennessee, Memphis, serving the population of Memphis, western Tennessee, and parts of Arkansas, and Mississippi. The study protocol was reviewed and approved by the Institutional Review Board of the University.

The study population consisted of 200 consecutive patients undergoing cesarean section for any indication. In the immediate postoperative period (usually within 1 hour, but occasionally as long as 4 hours post operatively), 5 ml of blood was drawn from the antecubital vein into a vacuum tube containing 0.05 ml of 15% ethylenediaminetetraacetic acid. All samples were then refrigerated until a Kleihauer-Betke acid elution test[10] could be performed to quantify the number of fetal cells present. All tests were performed within 24 hours of specimen collection by the same technician. One specimen was lost, leaving 199 patients for analysis.

The total amount of fetal blood present in the maternal circulation at the time of sampling was determined by the formula:

$$\frac{\text{Number of fetal cells}}{\text{Number of maternal cells}} = \frac{\text{Volume of fetal hemorrhage}^{10}}{\text{Maternal blood volume (estimate)}}$$

Maternal blood volume was estimated on the basis of maternal weight at the time of admission for cesarean section.

Patients were grouped according to amount of fetomaternal hemorrhage detected. In addition, the patients were divided into subgroups by indication for cesarean section to detect any effect of this factor on the incidence of significant fetomaternal hemorrhage.

The χ^2 analysis was performed to compare the rates of significant fetomaternal hemorrhage among subgroups.

Results

A total of 199 patients were available for analysis. Gestational age ranged from 26 to 43 weeks, with 156 patients (78.4%) having attained at least 36 weeks' gestation. Rh status was available in 180 patients. Of these, 156 (86.7%) were Rh positive and 24 (13.3%) were Rh negative.

Cesarean section was performed for the following indications: elective repeat in 23 (11.6%), fetal distress in 62 (31.1%), secondary arrest of labor—cephalopelvic disproportion in 60 (30.2%), breech or other malpresentation in 19 (9.5%), and other indications including placenta previa, abruptio placentae, fetal anomalies, and active herpes simplex virus infection in 32 (16.1%). In three cases (1.5%), the indication for cesarean section was unclear. These patients are included in the "other" group for analysis.

A total of 162 patients (81.4%) had no detectable fetomaternal hemorrhage, 27 (13.6%) had between 1 and 25 ml of fetomaternal hemorrhage; 5 (2.5%) had between 25 and 30 ml, and an additional 5 patients (2.5%) had >30 ml of fetomaternal hemorrhage detected. Clinical characteristics of the patients demonstrating >30 ml of fetal blood in the maternal compartment are shown in Table I.

Table II reveals the degree of fetomaternal hemorrhage by indication for delivery. Rates of significant fetomaternal hemorrhage by subgroup are not statistically different from one another.

Comment

The overall rate of detectable fetomaternal hemorrhage in our study populaton was 37 of 199 or 18.6%. Overall, in 2.5% of our patients there was evidence of a larger fetomaternal hemorrhage than would be neutralized by a single 300 μg dose of Rh immune globulin (i.e., >30 ml).[2] In addition, another 2.5% of patients had between 25 and 30 ml of hemorrhage—a group that may be at borderline risk of sensitization if given a single dose of Rh immune globulin. Ness et al.[8] reported an overall rate of detectable fetomaternal hemorrhage of 12.3% in cesarean section patients, with a rate of 2.8% for hemorrhage in excess of 20 ml.

Population studies have suggested that 0.6% to 1% of patients have significant fetomaternal hemorrhage detected post partum.[8, 9, 11] It remains unclear whether it is cesarean section itself or the antenatal factors predisposing the patient to operative delivery that result in the observed increase in significant fetomaternal hemorrhage. Pilkington[6] found an increased number of fetal cells before delivery in patients who subsequently underwent cesarean delivery, suggesting that the indication for surgery, rather than the procedure

Table II. Breakdown of degree of fetomaternal hemorrhage by indication for cesarean section

Indication	*Amount of fetomaternal hemorrhage*								
	0		*1-25 ml*		*25-30 ml*		*>30 ml*		
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Total*
Repeat	18	78.3	4	17.4	0	0	1	4.3	23
Fetal distress	49	79	7	11.3	3	4.8	3	4.8	62
Cephalopelvic disproportion	52	86.7	7	11.7	1	1.7	0	0	60
Breech	15	78.9	2	10.5	1	5.3	1	5.3	19
Other	28*	80	7	20	0	0	0	0	35*
TOTAL	162	81.4	27	13.6	5	2.5	5	2.5	

*Includes three cases in which indication was unclear.

itself predisposed the patient to an increased fetomaternal hemorrhage.

It is routine practice at our institution to deliver the placenta by manual extraction when performing a cesarean section. Although many groups studying the influence of obstetric factors on the incidence of fetomaternal hemorrhage have found manual removal of the placenta to increase the risk,[3-7] this has generally been studied after vaginal delivery. It is unclear whether this technique used at the time of cesarean section has any independent effect on the rate of fetomaternal hemorrhage over and above that that may be related to the operative delivery itself.

Fetal distress has also been associated in some reports with an increased incidence of significant fetomaternal hemorrhage.[3, 4, 7] In our study, cesarean section for fetal distress was not associated with any increased risk of significant fetomaternal hemorrhage compared with other indications for operative delivery. In fact, comparison of all the groups failed to reveal any significant difference in detectable hemorrhage or large fetomaternal hemorrhage between the various indications for operation.

Although the majority of our patients were Rh positive (86.7%) and therefore not at risk for Rh sensitization, it is unlikely that this factor would alter the amount of fetomaternal hemorrhage occurring at the time of delivery. ABO blood group incompatibility between mother and fetus is known to influence the likelihood of recovering fetal cells in the maternal circulation post partum.[5, 6] We were unable to confirm the ABO types of a sufficient number of our mother-infant pairs to be able to analyze this factor. If there was a delay in obtaining blood samples, ABO incompatibility would decrease the yield of fetal cells on Kleihauer-Betke analysis and therefore lead to an overall underestimation of the degree of hemorrhage. However, the fact that all study specimens were drawn within 4 hours of delivery minimizes any possible confounding effect of this factor.

The patients who demonstrated between 25 and 30 ml of fetal hemorrhage accounted for 2.5% of our study population. Because the error in the technique of quantifying fetal cells can be reasonably assumed to be ± 10%, there are patients in this group who would remain at risk for sensitization if administered only one vial of Rh immune globulin. Although the absolute risk of sensitization in these patients is small, an extra dose of Rh immune globulin would be prudent.

The Kleihauer-Betke acid elution test is a relatively sensitive test for the quantification of fetal bleeding.[12] However, it is labor intensive and even with careful standardization may result in widely varying results. Despite these drawbacks, it is currently the standard test and is used in the majority of clinical institutions and in published reports. New rapid tests for the detection of fetal cells including enzyme-linked antiglobulin tests[13] and a rosetting technique with enzyme-treated indicator erythrocytes[14] have been developed. These could be useful for widespread screening, with the Kleihauer-Betke test available for confirmation.

In 1984, the American College of Obstetricians and Gynecologists issued a recommendation that all Rh-negative women delivered of Rh-positive infants and in a high-risk category be investigated for quantification of fetomaternal hemorrhage post partum.[15] These high-risk categories included abruptio placentae, placenta previa, cesarean delivery, intrauterine manipulation, or manual removal of the placenta. Our study certainly supports the need for postpartum screening in Rh-negative patients undergoing cesarean section, with administration of extra Rh immune globulin to those who demonstrate excessive fetomaternal hemorrhage.

We conclude that in our population of 199 patients undergoing cesarean delivery for all indications, 2.5% had evidence of fetomaternal hemorrhage >30 ml at the time of delivery and an additional 2.5% had between 25 and 30 ml of hemorrhage.

On the basis of these findings, we recommend that all Rh-negative women delivered by cesarean section of Rh-positive infants undergo evaluation for quantification of fetomaternal hemorrhage. This testing should be performed early in the postpartum period to allow

for the administration of the appropriate protective dose of Rh immune globulin.

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Prediction of risk for preterm delivery by ultrasonographic measurement of cervical length

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Risk assessment for preterm delivery remains difficult, particularly among women with no prior history of preterm birth. We hypothesized that accurate assessment of cervical length by endovaginal ultrasonography could predict preterm delivery risk. A total of 178 patients with singleton gestations and without cervical incompetence were studied with transabdominal ultrasonography and endovaginal ultrasonographic cervical length measurement and manual vaginal examination of cervical length. A total of 113 patients who were evaluated by 30 weeks' gestation (excluding four induced preterm deliveries) were analyzed. Preterm delivery risk was compared between women with cervical lengths equal to or greater than the median and those with cervical lengths less than the median. An endovaginal ultrasonographic cervical measurement <39 mm was associated with a significantly increased risk of preterm delivery (25.0% versus 6.7%) and detected 76% of preterm births. Manual examination of cervical effacement detected 71% of preterm births, but transabdominal ultrasonographic measurement of cervical length was not preditive. Endovaginal ultrasonographic cervical measurement predicted increased preterm delivery risk regardless of parity or obstetric history. Endovaginal ultrasonography is a promising method for the prediction of risk of preterm birth. Because it has the potential to be an objective measure of cervical length, endovaginal ultrasonography may be superior to manual digital examination for preterm delivery risk assessment. (Am J Obstet Gynecol 1990;163:859-67.)

Key words: Cervix, preterm delivery, endovaginal ultrasonography, transabdominal ultrasonography, risk prediction

Several studies have noted that preterm delivery is more common among women with premature cervical effacement.[1-4] Despite these findings, cervical assessment has not become a routine approach for preterm delivery risk assessment. In part this may be a result of a lack of standardization of methods and difficulty in interpreting results of examinations by different persons.

Ultrasonographic examination has the potential to provide precise, objective, and repeatable measurements of cervical length. With the advent of endovaginal ultrasonography, it is possible to measure cervical length without the confounding effect of bladder filling. In earlier work we showed that endovaginal ultrasonography can provide precise measurements of cervical length.[5] Measurements of cervical length by transabdominal ultrasonography had more scatter throughout gestation than that of endovaginal ultrasonographic measurements. Furthermore, bladder filling improved visualization of the cervix, but artificially lengthened cervical measurements made by transabdominal ultrasonography.[5]

Patients who had cervical evaluation were followed up to delivery to compare risk of preterm birth relative to cervical length measurements made by transabdominal ultrasonography, endovaginal ultrasonography, and manual examination of the cervix. We hypothesized that cervical shortening (effacement) is associated with increased risk of preterm delivery, and that endovaginal ultrasonography measurement of cervical length provides a better estimate of preterm delivery risk than that of other approaches to cervical evaluation.

Methods

Women first seen for routine obstetric ultrasonographic examination from April 1988 through January 1989 were recruited for study. Patients with cervical incompetence or multiple gestation were excluded. Cervical incompetence was determined by history or by physical examination finding of silent cervical dilatation in the early second trimester. Each patient underwent a transabdominal ultrasonographic measure-

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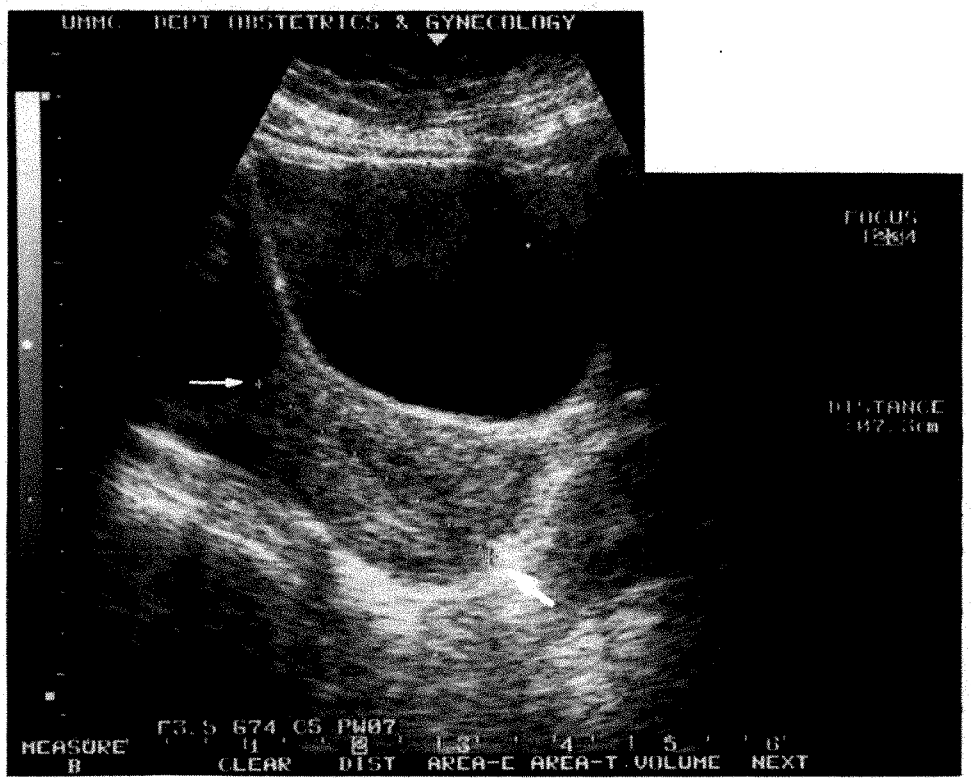


Fig. 1. Transabdominal ultrasonography of uterine cervix. *Small arrow*, internal cervical os; *large arrow*, external cervical os.

ment of cervical length, endovaginal ultrasonographic cervical length measurement (after emptying her bladder), and a manual vaginal examination of the cervix (unless contraindicated by placenta previa or patient refusal). Some patients had more than one scan performed, but only the first scan with complete data was used. All examinations were performed by the same examiner (H. F. A.).

Scans were performed with an Aloka 650 ultrasonography unit (Aloka Co., Ltd., Japan). Transabdominal cervical measurement was performed with a 3.5 MHz curvilinear probe. The cervix was visualized and the distance from internal to external os was measured (Fig. 1). Women were asked not to void for 1 to 2 hours before examination, but a full bladder was not required. Bladder dimensions (vertical and horizontal diameters) were measured and a subjective estimate of bladder filling (empty, partial, full) was recorded.

After the patient emptied her bladder, endovaginal probe cervical measurement was made with a 5 MHz vaginal probe attached to the Aloka 650 unit. The internal cervical os was visualized in the sagittal plane and the probe was manipulated until the entire cervical canal could be visualized. Markers were placed at the furthest points at which the cervical canal walls were juxtaposed and the cervical length was measured (Figs. 2 and 3). In some cases the cervix was too long to be entirely visualized in one scan. In these instances, a suitable structure such as a mucous cyst was used as a reference point and measurements were made from the internal os and the external os to the reference point and then added. Ultrasonographic measurements were performed twice by each method and the mean of the two measurements was used for each method.

After the ultrasonographic examination, manual examination was performed by estimating the length from the external cervical os to the cervical-uterine junction, as palpated through the vaginal fornix. The cervical canal was not probed by the examining finger.

Cervical length data were not reported to the patient's obstetric care provider. Informed consent was obtained for this study, which was approved by the institutional review board.

After delivery, charts were reviewed for pregnancy outcome, age, and obstetric index (number of prior term deliveries, preterm deliveries, and abortions). Estimated date of confinement was determined by the best obstetric estimate, which included menstrual data, clinical evaluation, and ultrasonographic examination. The

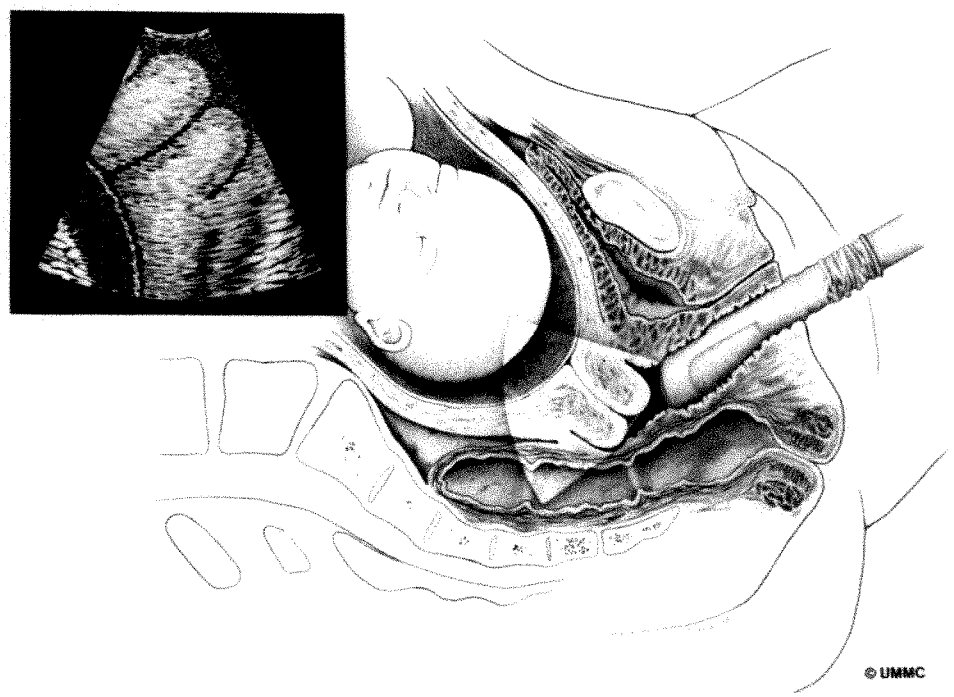


Fig. 2. Diagram of method to visualize uterine cervix with endovaginal ultrasonography. Inset represents ultrasonographic picture.

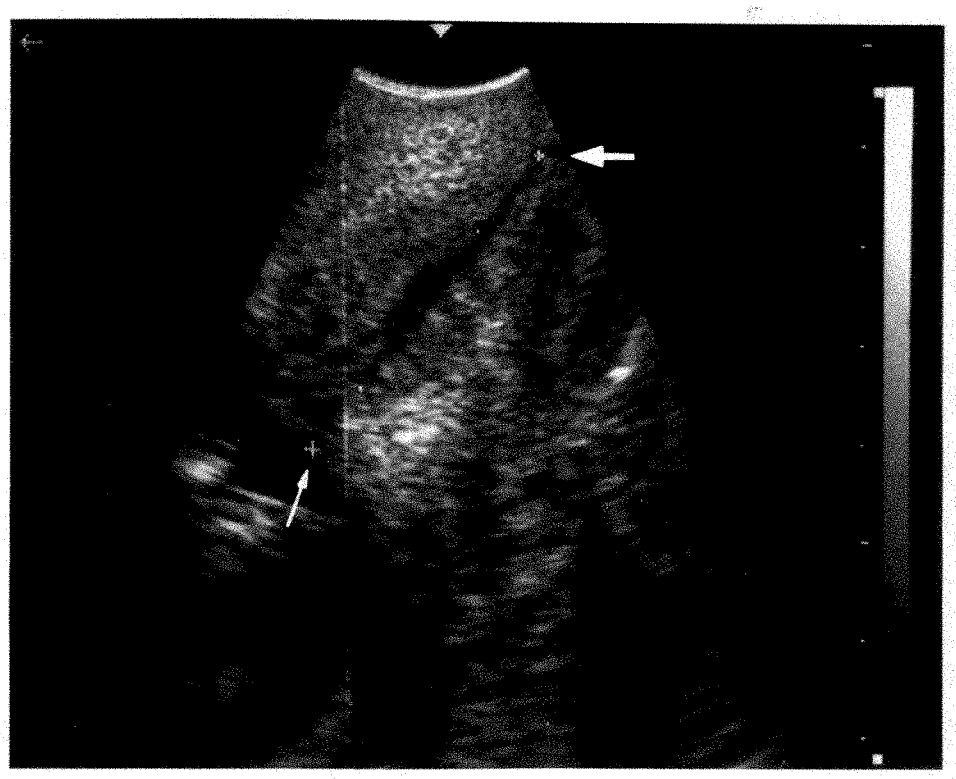


Fig. 3. Endovaginal ultrasonography of uterine cervix. *Small arrow,* internal cervical os; *large arrow,* external cervical os. Cervical length is measured as length of juxtaposed cervical canal walls.

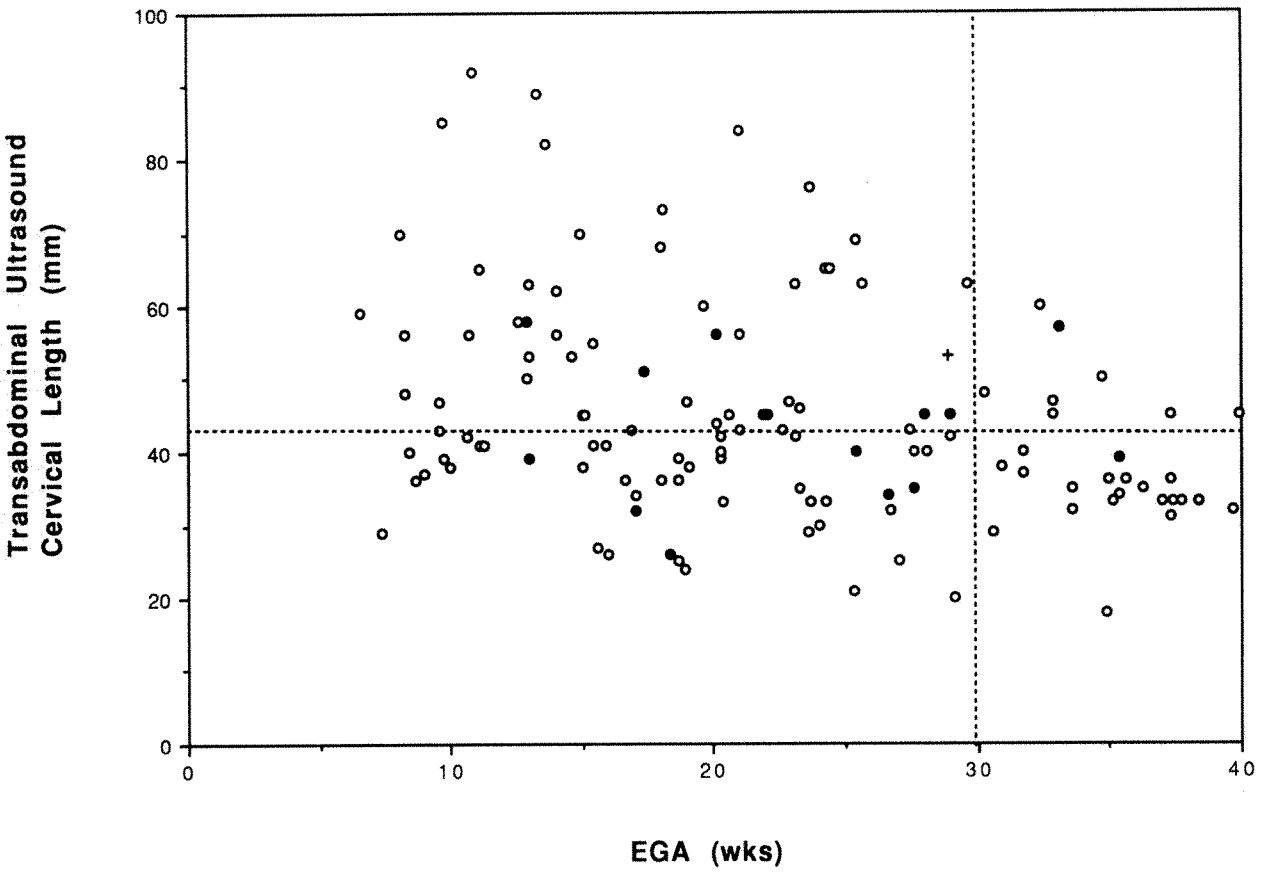


Fig. 4. Scattergram of transabdominal ultrasonographic measurements of cervix throughout gestation. *Open circles*, term delivery; *filled circles*, spontaneous preterm delivery; +, induced preterm delivery. *Horizontal dashed line* represents median cervical length for measurements made by 30 weeks' estimated gestational age *(vertical dashed line)*.

estimated date of confinement was used to determine estimated gestational age at the time of cervical measurement and at delivery. Preterm delivery was defined as delivery before 37 completed weeks' gestation (259 days).

Because of progressive shortening of average cervical length after 30 weeks' gestation, statistical evaluation was restricted to patients examined by 30 completed weeks' estimated gestational age. Data were analyzed with a standard microcomputer statistical package.[6] Statistical comparisons were made with the Student t test for comparisons of mean cervical length and χ^2 analysis of risk of preterm delivery. A p value <0.05 was used to reject the null hypothesis of no difference.

Results

A total of 178 women with singleton gestations and without cervical incompetence were evaluated. Ten patients were lost to follow-up (three first-trimester abortion, seven delivered elsewhere). Four patients had induced preterm delivery (indications: Rh isoimmunization, severe intrauterine growth retardation, and preeclampsia) and were excluded from evaluation. Figs. 4, 5, and 6 present graphs of measurements by the three methods throughout gestation. By all three methods there appears to be progressive shortening of average cervical length after 30 weeks' gestation. Horizontal dashed lines represent the median (50th percentile) for cervical length measurements by 30 weeks' estimated gestational age. Visual analysis suggests that the majority of preterm deliveries occurred in patients with endovaginal ultrasonographic or manual examination cervical measurements below the median; however, preterm patients are evenly scattered above and below the median for abdominal ultrasonographic measurements.

A total of 113 patients had cervical length measurements made by 30 weeks' gestation. Norms for cervical length through 30 weeks' gestation are shown in Table I. Abdominal ultrasonographic cervical measurement

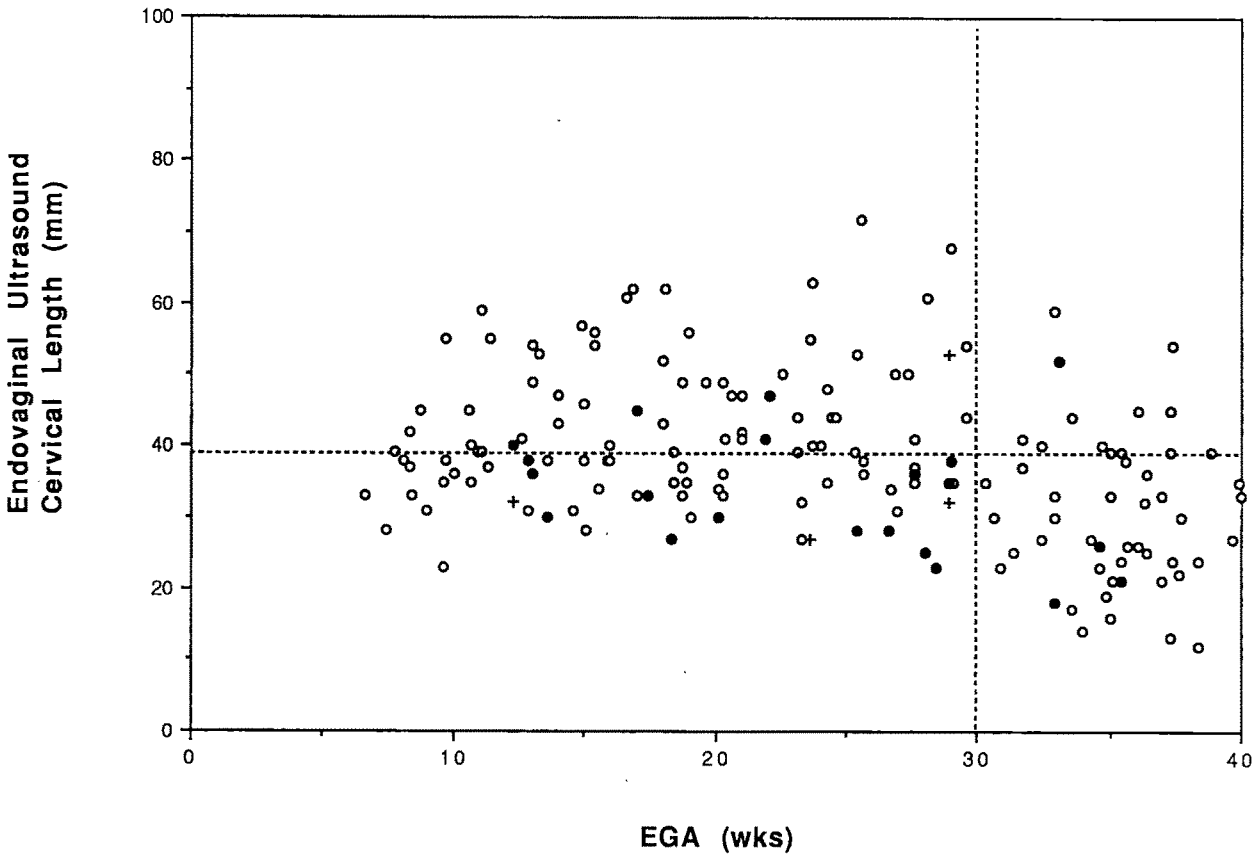


Fig. 5. Scattergram of endovaginal ultrasonographic measurements of cervix throughout gestation. *Open circles,* term delivery; *filled circles,* spontaneous preterm delivery; +, induced preterm delivery. *Horizontal dashed line* represents median cervical length for measurements made by 30 weeks' estimated gestational age *(vertical dashed line).*

was not possible in 6.2% of patients because of poor visualization of the cervix as a result of incomplete bladder filling. In one patient endovaginal ultrasonographic measurement was not possible because of severe constipation.

Comparison of mean cervical length of patients who were delivered of infants preterm and at term is presented in Table II. By each method mean cervical length was shorter among patients who were delivered preterm, but only measurements made with endovaginal ultrasonography or manual examination were statistically significant.

Sensitivity, specificity, and predictive values were determined for each method with cutoff values that represented the 50th and 25th percentiles for the range of measurements found through 30 weeks' gestation. The data are presented in Table III. The relative risk of preterm delivery in women with cervical shortening below the 50th percentile was 3.7 compared with that of women with cervical length longer than the 50th percentile. Cervical shortening below the 50th percentile by manual examination resulted in a 2.9-fold increased risk of preterm delivery. Cervical shortening measured by transabdominal ultrasonography was not statistically significantly related to preterm delivery risk, although shortening below the 25th percentile did result in a nearly twofold increased risk of preterm delivery.

Logistic regression analysis of risk of preterm delivery by cervical length measured by endovaginal ultrasonography showed a progressive and statistically significant trend toward higher risk of preterm birth with shorter cervical length (Fig. 7). Endovaginal ultrasonographic cervical assessment was compared in nulliparous women, multiparous women without prior preterm delivery, and multiparous women with a history of preterm delivery (Table IV). The overall results were statistically significant, although individual categories of obstetric history contained too few numbers to reach significance separately.

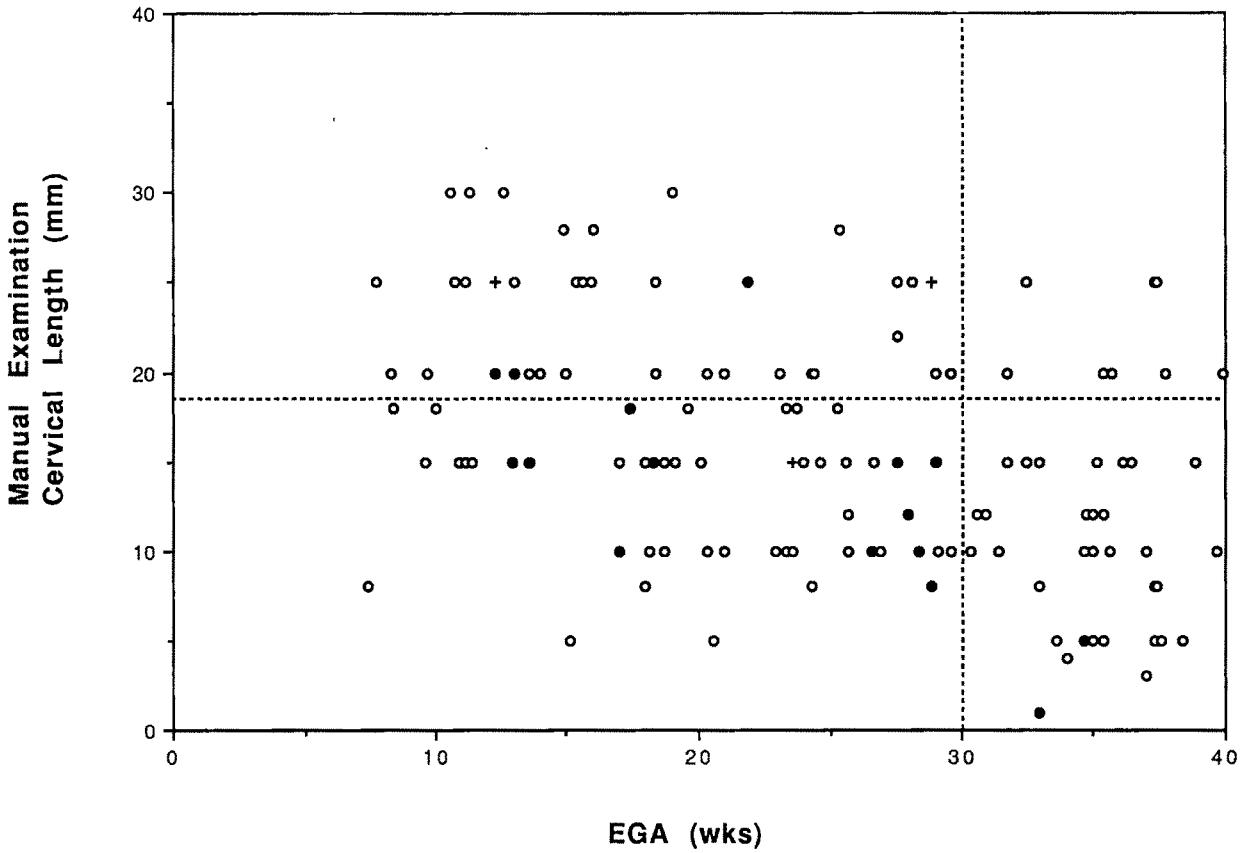


Fig. 6. Scattergram of manual vaginal examination measurements of cervix throughout gestation. *Open circles,* term delivery; *filled circles,* spontaneous preterm delivery; +, induced preterm delivery. *Horizontal dashed line* represents median cervical length for measurements made by 30 weeks' estimated gestational age *(vertical dashed line).*

Table I. Norms for cervical length among 126 patients without incompetent cervix, who had cervical length measurement by 30 weeks' estimated gestational age

	ABDCX	*VAGCX*	*MANCX*
Number	106	125	97
Mean (mm)	46.8	40.9	17.9
SD	15.3	10.0	6.4
50th percentile (mm)	43	39	18
25th percentile (mm)	36	34	15
10th percentile (mm)	29	30	10

ABDCX, Transabdominal ultrasonographic cervical length measurements; *VAGCX,* endovaginal ultrasonographic cervical length measurement; *MANCX,* manual examination cervical length measurement.

Comment

Risk assessment for preterm delivery continues to be a difficult problem in obstetrics. Numerous investigators have developed or modified risk scoring systems for preterm birth, but results have been variable.[7-10] Not infrequently, promising results by one investigator are not confirmed by others with the same system.[11,12] However, most risk assessment studies have noted that premature cervical effacement is associated with an increased risk of preterm delivery.

Independent studies of cervical effacement and dilatation have confirmed the association with preterm delivery.[1-4] This contrasts with older studies that suggested that cervical effacement and dilatation is a common occurrence as pregnancy progresses.[13-15] These earlier studies tend to frustrate cervical assessment in women at risk for preterm labor because some clinicians believe that cervical change is a normal phenomenon. Furthermore, differences among individual examiners makes standardization of findings difficult.

Ultrasonography and particularly endovaginal ultrasonography has the potential to provide objective, repeatable cervical length measurements. The vaginal scanning approach has several advantages over the

Table II. Comparison of cervical length measurements between patients who were delivered of infants preterm and at term*

	Term delivery			*Preterm delivery*			
	No.	*Mean (mm)*	*SD*	*No.*	*Mean (mm)*	*SD*	*p Value (Student t test)*
ABDCX	83	47.8	16.3	13	42.4	9.4	0.10
VAGCX	95	42.8	9.9	17	34.1	6.9	0.001
MANCX	72	18.2	6.6	14	14.8	4.7	0.04

ABDCX, Transabdominal ultrasonographic cervical length measurement; *VAGCX,* endovaginal ultrasonographic cervical length measurement; *MANCX,* manual examination cervical length measurement.

*All patients had cervical length measurement by 30 weeks' estimated gastational age.

Table III. Risk of preterm delivery among patients grouped by cervical length cutoffs of the 50th percentile and 25th percentile for cervical length

	Cutoff		*≥Cutoff*		*<Cutoff*				
			Risk of preterm delivery		*Risk of preterm delivery*				
	Percentile	*Length (mm)*	*%*	*n*	*%*	*n*	*Sensitivity (%)*	*Specificity (%)*	*p Value (χ^2)*
ABDCX	50	43	13.7	51	13.3	45	46	53	NS
	25	36	11.8	76	20.0	20	31	81	NS
VAGCX	50	39	6.7	60	25.0	52	76	59	0.01
	25	34	10.1	89	34.8	23	47	84	0.003
MANCX	50	18	8.7	46	25.0	40	71	58	0.04
	25	15	14.1	64	22.7	22	36	76	NS

ABDCX, transabdominal ultrasonographic cervical length measurement; *VAGCX,* endovaginal ultrasonographic cervical length measurement; *MANCX,* manual examination cervical length measurement.

transabdominal method for evaluation of the cervix. With an empty bladder about half of cervical length measurements are not possible because of inadequate visualiztion of the cervix, but bladder filling significantly lengthens the measured cervical length.[5, 16, 17] Endovaginal scanning with an empty bladder removes a major confounding factor in the assessment of cervical length and visualization of the cervix is possible in nearly all patients. It is interesting that mean cervical lengths determined by endovaginal ultrasonography are similar to those found by Zemlyn, Varma, and Bowie[18-20] in studies that evaluated the cervix by transabdominal ultrasonography with an empty or nearly empty bladder.

Although several studies of ultrasonographic cervical evaluation have concentrated on demonstration of cervical incompetence, the principal ultrasonographic indication of cervical incompetence is dilatation of the endocervical canal with prolapse of amniotic membranes.[21-23] Two investigators have suggested that cervical shortening is indicative of cervical incompetence.[24, 25] These authors excluded women whose pregnancies ultimately resulted in preterm birth; therefore, their findings cannot be directly compared with ours. In an earlier study of a small group of women with clinically demonstrated incompetent cervix, we failed to find a significant difference in cervical length.[5]

Our results confirm that premature cervical effacement is associated with an increased risk of preterm delivery. More specifically, risk of preterm delivery is inversely proportional to cervical length and increases significantly with shorter cervical length measurements. It appears that risk detection by cervical length measurement works well in nulliparous women and women without prior preterm deliveries, groups that have been difficult to adequately assess for risk of preterm delivery. In this study endovaginal ultrasonographic measurement was clearly superior to transabdominal ultrasonographic measurement in the prediction of preterm delivery risk. It is important to note that this study was cross-sectional, that is, each patient was included only once. That makes our data applicable for screening a

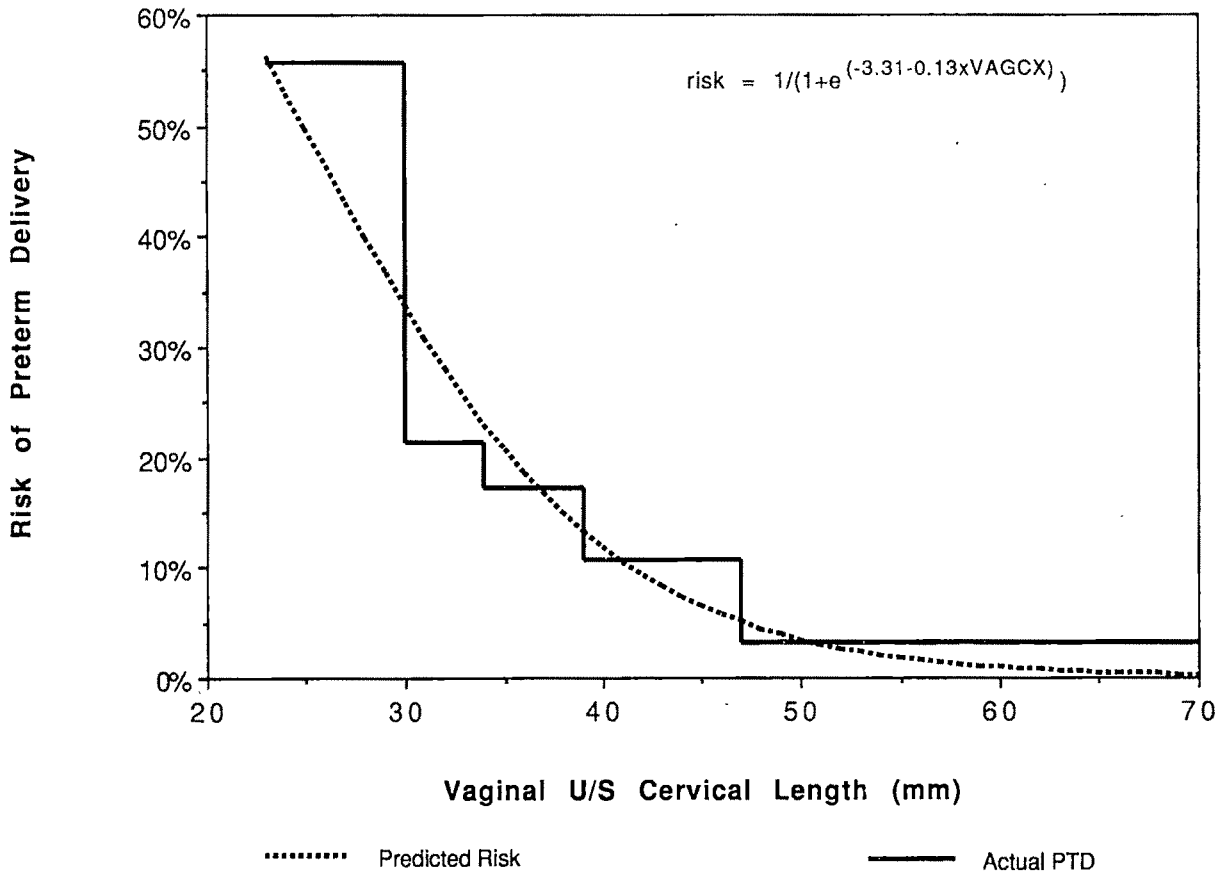


Fig. 7. Logistic regression analysis of risk of preterm delivery by cervical length measured by endovaginal ultrasonography. *Solid line,* actual preterm delivery rate; *dashed line,* predicted risk by regression equation.

Table IV. Prediction of preterm delivery risk with endovaginal ultrasonography by parity and obstetric history

	Nulliparous patients	*Multiparous patients*	
VAGCX	—	Term only	History of preterm delivery
≥39 mm	5.6% (18)	2.9% (24)	25.0% (4)
<39 mm	12.5% (24)	25.0% (16)	50.0% (12)

$p = 0.015$ (Mantel-Haenszel χ^2). *VAGCX,* Endovaginal ultrasonographic cervical length measurement. Number of patients in parentheses.

population of pregnant women; but these data do not answer the question of the significance of change in the cervical examination.

Manual examination also showed a significant association between cervical shortening and preterm delivery risk. Cervical dilatation was not evaluated in this study because we prefer to avoid probing the cervical canal to the level of the internal os. All examinations were performed by a single examiner after the ultrasonographic examination, raising the possibility of bias in the measurement. Furthermore, the comparability of cervical examinations among multiple examiners was not tested. Further study is needed to better quantify the value of manual cervical examination.

The mechanism of cervical effacement is not well understood, but involves a complex biochemical and structural reorganization of the connective tissue of the cervix. Although the nature of the relationship between myometrial contractions and cervical effacement is not known, it is clear to the clinician that contractions and

cervical change are closely linked. Recent work by Main, et al.[26] has suggested that increased uterine contractions detected during routine monitoring at prenatal visits detects patients at increased risk of preterm delivery. That finding, coupled with our work, suggests that physiologic indicators of preterm labor may be identifiable and useful in risk assessment.

This study shows a relationship between cervical shortening and preterm delivery risk. We cannot recommend an optimum cutoff point for cervical length to predict preterm delivery risk. It is important to note that this study needs to be validated by further investigations involving multiple examiners and other populations. In addition, more study is needed to evaluate the cervix in a longitudinal fashion throughout pregnancy, and to examine the combination of two or more examination modalities as predictors of preterm delivery.

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Is indicated or spontaneous preterm delivery more advantageous for the fetus?

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We performed a case-control study to determine whether fetuses delivered prematurely because of pregnancy complications (primarily pregnancy-associated hypertensive disease) had a different neonatal course than that of those born after either spontaneous preterm labor or after premature rupture of the membranes. Two case-control populations were matched by gestational age at delivery, fetal sex, and race. There was no perinatal survival advantage in babies delivered from "stressed" pregnancies. Selected neonatal morbidities were generally similar, but there was an increased incidence of necrotizing enterocolitis in babies born after preterm labor and a higher incidence of both necrotizing enterocolitis and neonatal sepsis after premature rupture of the membranes. We conclude that a "stressed" pregnancy confers a negligible survival advantage to the fetus (AM J OBSTET GYNECOL 1990;163:868-72.)

Key words: Perinatal survival, fetal lung maturation, preterm labor, complicated pregnancy

Numerous studies support a relationship between pregnancy complications and accelerated fetal pulmonary maturation.[1] One explanation for this phenomenon is that the fetus responds to a "stressed" environment by increasing its adrenal glucocorticoid production. This leads to earlier production of surface active phospholipids in the fetal lungs.[6] Whereas the laboratory evidence of accelerated pulmonary maturation in certain complicated pregnancies (especially pregnancy-associated hypertensive diseases) is compelling, not all authors agree.[7-9] This disagreement may be a result of differences in the biochemical markers used to define the accelerated maturation, differences in the definition of "stressed pregnancies," and possibly the control patients used for comparison. Nevertheless the implication is that babies delivered prematurely from complicated pregnancies have a survival advantage compared with their counterparts delivered as a result of spontaneous, idiopathic preterm labor. We could find little data to support this common clinical assumption.[10]

Because respiratory distress syndrome and its sequelae are the leading causes of neonatal mortality in the United States,[11] it seems plausible that any factor, such as "intrauterine stress," that may decrease the incidence of hyaline membrane disease would improve the neonatal course. We therefore performed a case-control study by comparing neonates whose mothers had an indicated preterm birth for maternal or fetal indications with two control populations. The first of these included neonates who were delivered as a result of spontaneous preterm labor with no prior membrane rupture, whereas the other group comprised neonates delivered prematurely after premature rupture of the membranes.

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Methods

Data were collected prospectively as part of a multicenter trial of preterm birth prevention funded by the March of Dimes at the University of Alabama Hospitals. During the study period from November, 1982, through April, 1986, all cases of preterm delivery between 20 and 36 weeks' gestation were identified by specially trained research nurses. Each maternal and neonatal record was then reviewed for specific information about the pregnancy, labor, delivery, and neonatal course. The data were collected onto standardized coding sheets and entered into a central computerized data base. The information recorded included demographic characteristics, underlying maternal disease states, use of tocolytic therapy or glucocorticoids, delivery method, and the specific reason for the preterm birth. The neonatal charts were abstracted for the presence of specified complications contained in the final discharge diagnoses approved by the responsible neonatologist. Infant ventilation time was coded in whole number of days, and one day was considered to be at least 12 hours. The presence and type of any recognized congenital anomalies were also recorded.

Both obstetric and neonatal gestational dating cri-

teria were reviewed by one of the principal investigators. Sonographic data are routinely obtained as part of our general obstetric care, and most of our study population had an early ultrasonographic examination to confirm our clinical gestational dating criteria.

Only those women who were delivered of a live-born infant between 24 and 36 weeks' gestation were included in the analysis. We defined a live-born infant as any baby who had a nonzero Apgar score at either 1 or 5 minutes. A perinatal death was defined as the death of a live-born infant before discharge from the hospital. Neonatal days in the hospital were counted from the day of birth until the baby was either discharged home or transferred to another facility.

The diagnosis of membrane rupture was usually made by the observation of vaginal pooling of amniotic fluid, which, after drying, showed the typical ferning pattern. The use and choice of tocolytic agents for patients with preterm labor were determined by the attending physician. Currently, premature membrane rupture is considered a contraindication to tocolytic therapy at our institution. However, during the term of this study, patients with ruptured membranes often received a brief (≤24-hour) course of parenteral magnesium sulfate. Each decision to effect an indicated preterm birth was made by the attending physician.

During this study period 1183 women were delivered of singleton, live-born infants between 24 and 36 weeks[3] gestation. None of these women had received antenatal glucocorticoid therapy. Furthermore, we excluded women whose newborn had a major organ system anomaly and women with rhesus isoimmunization, insulin-dependent diabetes mellitus, homozygous hemoglobinopathies, or sepsis. Application of these criteria yielded a population of 1015 gravidas. Of these, 202 women had an indicated preterm delivery, 537 were delivered after spontaneous preterm labor, and 276 were delivered after premature rupture of the membranes (PROM). A total of 178 women with an indicated preterm delivery were matched to women with a spontaneous preterm delivery on the basis of gestational age in completed weeks, maternal race, and fetal sex. In like manner, 159 women with an indicated preterm delivery were able to be matched to a group of women with preterm membrane rupture and delivery. Women with an indicated preterm delivery who were matched with those with preterm labor were, by design, not identical to those with an indicated preterm delivery who were matched with a group of women with PROM. Therefore, separate analyses were performed on the two match-paired, case-control groups.

Data were analyzed with the SAS (Statistical Analysis System, Carey, N.C.) software release 6.01 for personal computers. The Student t test, the χ^2 test of proportions, the Fisher exact test, and the Wilcoxon rank-sum test for nonparametric data were used where appropriate.

Table I. Indications for preterm delivery

Indications	*Indicated preterm delivery versus preterm labor (N = 178)*		*Indicated preterm delivery versus PROM (N = 159)*	
	No.	*%*	*No.*	*%*
Maternal hypertension	121	68	112	70
Abruptio placentae	18	10	15	10
Placenta previa	10	6	6	4
Other*	29	16	26	16
TOTAL	178		159	

IPD, Indicated preterm delivery; *PTL,* preterm labor.
*Abnormal antepartum testing, oligohydramnios, suspected growth retardation.

Results

The primary delivery indications for the two populations with indicated preterm delivery are listed in Table I. In some cases more than one indication was present. When this occurred, the indication considered to be the proximate cause of the delivery was chosen; we did not analyze these patients separately. The two populations with indicated preterm delivery populations were similar but not identical, and the majority of indicated preterm births were for maternal hypertensive conditions.

Selected population characteristics for the indicated preterm delivery versus preterm labor and indicated preterm delivery versus PROM groups are shown in Tables II and III. Because of the matching criteria, the mean gestational ages and proportions of nonwhite gravidas were identical. However, the patients with indicated preterm delivery were significantly older and contained a higher proportion of nulliparous patients. In addition, women in the preterm labor and PROM control groups were more likely to have labored, to have undergone a vaginal delivery, and to have received parenteral tocolytic agents during their pregnancy. Small proportions of the patients with indicated preterm delivery (13 of 159 and 15 of 178) received tocolytic agents. Most of these women were first seen with vaginal bleeding and preterm contractions. These patients received a brief course of parenteral tocolytic therapy during initial evaluation until the clinical diagnosis of abruptio placenta or placenta previa was con-

Table II. Population characteristics, indicated preterm delivery versus preterm labor ($N = 178$)

	Indicated preterm delivery	*Preterm labor*	*p Value*
Maternal age (yr)	25	22	<0.001
Nulliparous (%)	48	34	0.007
Nonwhite (%)	73	73	NS
Labored (%)	58	100	<0.001
Vaginal delivery (%)	40	85	<0.001
Intravenous tocolysis (%)	8	30	<0.001
Mean gestational age (wk)	33.7	33.7	NS
Mean birth weight (gm)	1981	2203	0.001
Small for gestational age (%)*	21.4	6.7	<0.001
Apgar score <3 at 5 min (%)	2.8	5.1	0.28

IPD, Indicated preterm delivery; *PTL,* preterm labor.
* <10th percentile.

Table III. Population characteristics, indicated preterm delivery versus PROM ($N = 159$)

	Indicated preterm delivery	*PROM*	*p Value*
Maternal age (yr)	25	23	0.01
Nulliparous (%)	50	31	0.001
Nonwhite (%)	78	78	NS
Labored (%)	57	96	<0.001
Vaginal delivery (%)	43	89	<0.001
Intravenous tocolysis (%)	8	41	<0.001
Mean gestational age (wk)	34	34	NS
Mean birth weight (gm)	2005	2224	0.001
Small for gestational age (%)*	22	6.3	<0.001
Apgar score <3 at 5 min	1.3	1.3	1.0

IPD, Indicated preterm delivery.
* <10th percentile.

firmed or mandated delivery. The remaining patients had received a course of tocolytic therapy before they were seen for an indicated delivery.

The babies with indicated preterm delivery were smaller and were more likely to be under the 10th percentile for birth weight according to the criteria of Brenner et al.[12] Selected neonatal outcomes are shown in Tables IV and V for the indicated preterm delivery versus preterm labor and indicated preterm delivery versus PROM matched groups of patients. Most importantly, the perinatal mortalities and the incidence of the respiratory distress syndrome were similar between the group with indicated preterm delivery and their respective control populations. In most other respects, the case and control neonates were not significantly different. However, the incidence of necrotizing enterocolitis was higher in both control groups, whereas the neonates delivered because of maternal PROM had significantly more neonatal sepsis. The neonates with indicated preterm delivery also had longer hospital stays (Wilcoxon rank-sum test), whereas the indicated preterm delivery and preterm labor neonates had a significantly higher incidence of hyperbilirubinemia.

Comment

This is the first case-control study of which we are aware that assesses the risk of neonatal mortality and selected morbidities resultant from an indicated preterm birth compared with those after spontaneous preterm labor or PROM. There was no survival advantage for infants delivered from the selected complicated pregnancies. The neonatal morbidity rates were also similar. However, both control groups had significantly more necrotizing enterocolitis and the PROM group had significantly more neonatal sepsis than that of their matched populations with indicated preterm delivery. The relationship between neonatal infectious morbidity and PROM has been clearly established.[13] Similarly, necrotizing enterocolitis may be partly a result of underlying infectious agents, and one might anticipate its occurrence more often after PROM. That it should occur more frequently after preterm labor with intact membranes is more obscure unless one considers that a sizable number of preterm labors are caused by subclinical infections or that the group with indicated preterm delivery had a fourfold greater incidence of cesarean deliveries. The stress of labor and contact with the genital flora may have been contributing factors. Compared with both control populations, the neonates in the group with indicated preterm delivery also required significantly more days in the hospital. This likely was related either to their smaller birth weights, inasmuch as discharge criteria usually demanded a weight of at least 2000 gm, or to their indicated maternal transport from remote locations.

Table IV. Neonatal outcome, indicated preterm delivery versus preterm labor ($N = 178$)

	Indicated preterm delivery	*Preterm labor*	*p Value*
Perinatal mortality (%)	5.6	6.2	0.59
Respiratory distress syndrome (%)	23.6	17.4	0.15
Ventilation time (days)	3.5	5.5	0.84
Hospital days	11.9	10.2	<0.001
Intraventricular hemorrhage (%)	1.7	3.4	0.31
Neonatal sepsis (%)	2.2	5.1	0.16
Necrotizing enterocolitis (%)	1.1	6.7	0.006
Patent ductus arteriosus (%)	6.2	10.1	0.18
Hypoglycemia (%)	6.2	4.3	0.48
Hyperbilirubinemia (%)	16.8	26.4	0.03

IPD, Indicated preterm delivery; *PTL,* preterm labor.

Table V. Neonatal outcome, indicated preterm delivery versus PROM ($N = 159$)

	Indicated preterm delivery	*PROM*	*p Value*
Perinatal mortality (%)	3.1	3.8	0.76
Respiratory distress syndrome (%)	20.8	15.1	0.18
Ventilation time (days)	4.2	5.5	0.09
Hospital days	11.5	7.9	0.001
Intraventricular hemorrhage (%)	0.6	1.3	0.56
Neonatal sepsis (%)	2.5	7.6	0.04
Necrotizing enterocolitis (%)	1.3	5.0	0.05
Patent ductus arteriosus (%)	5.7	3.8	0.42
Hypoglycemia (%)	6.3	6.9	0.82
Hyperbilirubinemia (%)	16.3	24.5	0.07

IPD, Indicated preterm delivery.

Whereas the patients with indicated preterm delivery and their control populations were matched by gestational age, race,[14] and fetal sex,[11] they were in some respects dissimilar. Although antenatal glucocorticoid therapy has been shown in most reports to decrease the incidence and severity of hyaline membrane disease with intact membranes, the relationship between glucocorticoid administration and respiratory distress syndrome in cases of PROM is more controversial.[15] Therefore, we did not include patients who had received betamethasone. In addition, we excluded from the control groups any women who had recognized maternal or fetal pathology that could have acted as an additional stress. Finally, we omitted from the populations with indicated preterm delivery any complications such as maternal diabetes mellitus or isoimmunization because of the controversies surrounding their effects on fetal lung maturation.[16]

Other possible sources of bias included the presence of labor,[4] delivery route,[17,18] and use of tocolytic agents.[19] Our data show that women first seen with spontaneous preterm labor and PROM are more likely to have a vaginal delivery than are those who have an indication for a preterm delivery. Because the risk of the development of respiratory distress syndrome may be significantly influenced by these factors,[16] they may have, in part, accounted for the similar neonatal outcomes. We also considered that our population with indicated preterm delivery may not have been sufficiently "stressed" or that delivery was effected before the beneficial effect of the intrauterine stress was complete. Because the mechanism and timing of this process are poorly characterized, it is possible that our collection of complicated pregnancies might not have contained enough severely stressed fetuses to show a difference. Gestational age may also be a factor in the development of accelerated pulmonary maturation, being more pronounced in certain gestational age ranges.[10] However, examination of the pregnancy outcomes on either side of 32 weeks' gestation showed similar results. The Apgar scores did not indicate that the neonates with indicated preterm delivery had an increased incidence of intrapartum asphyxia, although this possibility was not entirely excluded. The relationship between fetal hypoxemia and complications of pregnancy are well described, and asphyxia may predispose neonates to the development of respiratory distress syndrome.[20] This could negate the beneficial effects of any previous chronic fetal stress.

We conclude that the fetal stress of pregnancy complications severe enough to warrant an indicated premature birth do not confer a neonatal survival advantage compared with babies whose mothers were delivered because of PROM or preterm labor. It is most likely that PROM and preterm labor themselves act to stress the fetus.

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Evaluation of a risk scoring system as a predictor of preterm birth in an indigent population

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A risk scoring system designed to predict spontaneous preterm birth was implemented in a large, indigent population as part of a multicenter trial of preterm birth prevention. A total of 7478 women with singleton gestations were screened and followed up prospectively at the Birmingham project center. Patients who had an indicated preterm delivery or a fetal anomaly were excluded from the study population. Analysis by assigned risk score and parity showed that, whereas the sensitivity and positive predictive value were better in multiparous women than in nulliparous women, overall the values were low. Logistic regression analyses of the multiparous and nulliparous populations showed independent sets of significant ($p \leq 0.05$) risk variables. A history of preterm delivery and a low prepregnancy weight were the most predictive risk factors in the multiparous and nulliparous models, respectively. We conclude that the clinical usefulness of a risk scoring system to predict spontaneous preterm birth in an indigent population is limited.
(AM J OBSTET GYNECOL 1990;163:873-9.)

Key words: Preterm birth, risk scoring system, premature labor

Preterm birth is one of the most significant health problems in the United States.[1] Neonatal management of low birth weight–infants has improved: methods to prevent premature birth have not. The causes of prematurity are complex, poorly understood, and remain under intensive investigation. In some cases, underlying maternal diseases, known to increase the likelihood of maternal or fetal compromise, may be recognized and treated early in pregnancy. Other conditions, such as preeclampsia, are often treated by preterm delivery. Whereas a portion of preterm deliveries are indicated for maternal or fetal conditions, the majority come after preterm labor with or without antecedent rupture of the membranes.

Previous authors[2-6] have sought to identify patients at high risk of preterm labor in an attempt to alter its natural history. Because many patients with preterm labor are seen too late for successful tocolytic therapy, the concept of early recognition of the signs and symptoms of preterm labor has been stressed. Central to these efforts has been a risk scoring system that comprises various factors that have a statistically significant relationship to preterm delivery.[7] One system devised by Papiernik has been popularized in this country by Creasy and others.[8] This system depends on the identification of individually weighted risk factors. The individual risk values are then tallied to produce a combined risk score and distinguishes low-risk from high-risk groups. Patients considered to be at high risk are given special attention during their antenatal course. This consists of education about the symptoms of preterm labor, frequent prenatal visits, and assessment of the signs of preterm labor (e.g., cervical dilatation). Stress reduction and correction of identified risk factors (e.g., cigarette smoking) has commonly been included in these programs.

To understand the potential usefulness of a risk scoring system, it should be viewed within the entire context of the preterm birth dilemma, the primary goal of which should be the prevention of neonatal morbidity and mortality (Fig. 1). Unless universal changes in prenatal care are adopted in an attempt to decrease the incidence of all preterm births, specific modifications to routine prenatal care depend on the accurate identification of those women who are at the highest risk of preterm labor. Therefore, to be clinically useful, a risk scoring system should have a high sensitivity, and to be cost effective, it should have a high positive predictive value. This study examines the clinical usefulness of a risk scoring system for the prediction of spontaneous preterm birth in a large, indigent population. Because many of the risk variables were applicable only to multiparous patients, we sought to confirm, as others

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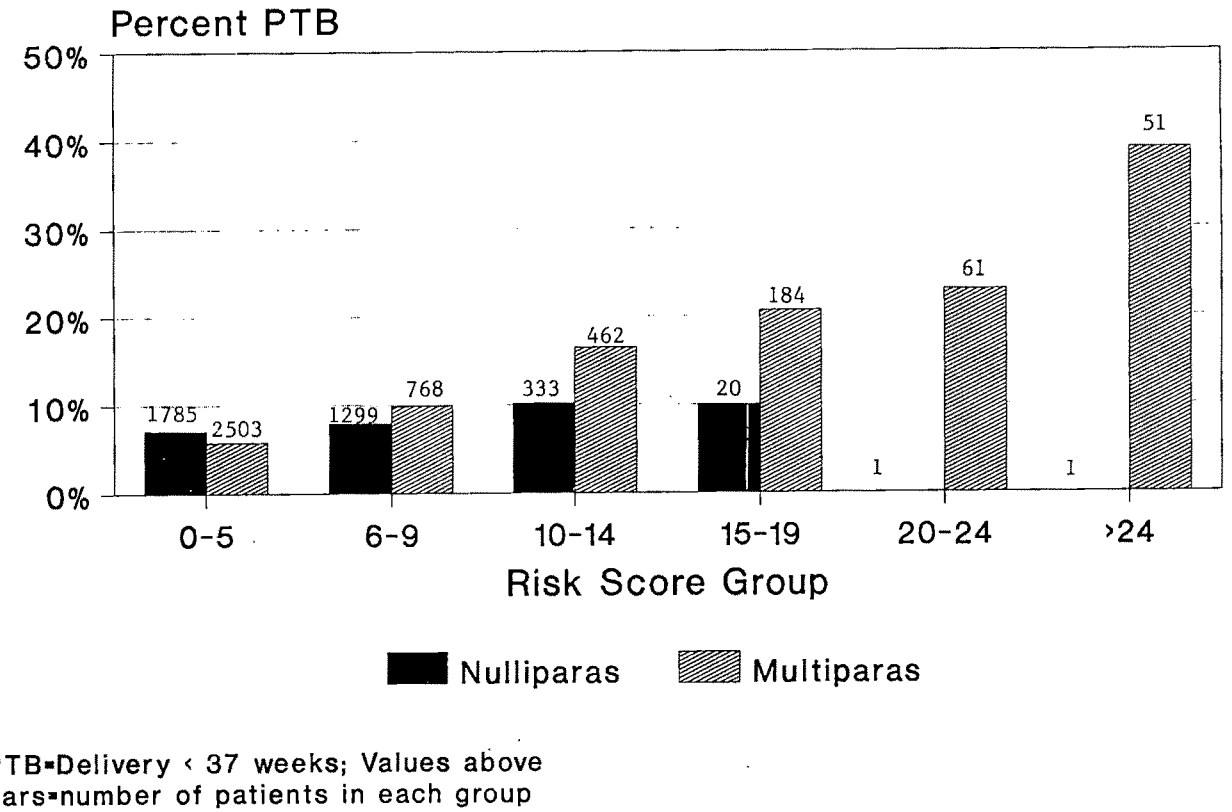


Fig. 1. The scope of neonatal morbidity and mortality prevention.

have shown,[3, 4] that the scoring system would have different predictive values in nulliparous versus multiparous patients.

Methods

As part of a multicenter trial of preterm labor prevention, women who registered in the Jefferson County Health Department system for obstetric care and who had an estimated date of confinement between August 15, 1983 and April 19, 1986 were screened for risk factors in accordance with a risk scoring system (Table I). However, patients at >30 weeks' gestation at the first visit were excluded. The initial evaluation and risk score assessment included 35 risk variables and was performed as soon as possible after the first prenatal visit. Women who were first seen for care before 22 weeks' gestation were reevaluated between 22 and 26 weeks and their scores were adjusted accordingly. Patients with total scores <10 were considered to be at low risk and were given the usual prenatal care. Routine prenatal care included screening for pregnancy complications and referral to our high-risk obstetric clinic when appropriate. Patients with scores ≥10 were offered entry into the prospective preterm birth prevention program staffed by specially trained nurse practitioners. The program stressed early patient and physician recognition of preterm labor, immediate evaluation of patients suspected to have preterm labor, and appropriate tocolytic therapy. Patients who agreed to participate were randomly assigned to either the intervention group or to a control group of women who received routine prenatal care. Patients who refused to participate or who were ineligible (e.g., inability to contact the patient in time for randomization) also received routine prenatal care. Patients who underwent the initial screening and risk assessment were followed up prospectively. Data were collected and recorded on standardized coding sheets by trained research personnel. These were entered into a central computerized data base. Although this data base contained information from each of the five project centers, for this report we chose to include only the project data on singleton pregnancies from our center (the Birmingham center). Our center entered and delivered nearly 40% of the clinical participants, thus, the uniform prenatal care within a single institution would improve the comparability of patient data with respect to management strategies. At our institution there was no significant difference in the incidence of preterm delivery between the intervention group and the control patients.[9] Therefore the intervention group was included in the analysis of the scoring system. Patients who had an indicated preterm delivery or a significant fetal anomaly were excluded from the analyses.

Table I. Risk scoring system

Individual risk variable scores					
1	*2*	*3*	*4*	*5*	*10*
Historic factors					
First-trimester losses = 1	Chronic hypertension	Height <152 cm	Age ≤17 yr	Second-trimester losses = 1	Each prior PTB*
Education 9-11th grade	Marital status single	Prepregnancy weight <45.5 kg	Pyelonephritis	Cone biopsy*	Each prior pregnancy with PTL and term birth*
Last birth <1 year*	First-trimester losses = 2	First-trimester losses >2		Uterine anomaly†	Second-trimester losses ≥2
	Education ≤8 grade			DES exposure†	
Factors associated with this pregnancy					
Preschool children at home*	Bacteriuria	Uterine fibroids	Bleeding after 12 wk	Oligohydramnios†	Multiple gestation†
Work outside of home	Poor weight gain	Febrile illness	Cervical length <1 cm†	Polyhydramnios†	Abdominal or cervical surgery†
	Age 18-19 yr or >40 yr	Weight loss	Internal os dilated*	Placenta previa†	
	Heavy work	Long commute†	Uterine irritability†		
	Proteinuria ≥1+	Presenting part engaged at 32 weeks†			
	Smokes >10 cigarettes/day				

PTL, Preterm labor; *PTB,* preterm birth; *DES,* diethylstilbestrol.
*Excluded from logistic regression analysis in nulliparas only (see Methods section).
†Excluded from logistic regression analysis in all patients (see Methods section).

Because the definition of preterm birth depends on accurate pregnancy dating, both obstetric and neonatal criteria were collected. The records of all patients who were delivered of infants before 37 completed weeks' gestation, in whom there was greater than a 2-week discrepancy between the obstetric and neonatal gestational age estimates, and who had babies weighing under 2750 gm were reviewed by one of the principal investigators before a final gestational age assignment was made. Because of the intake scheduling, most of our patients had an early ultrasonographic examination.[10] We defined delivery before 37 completed weeks' gestation as a preterm birth and delivery before 32 completed weeks' gestation as a very preterm birth.

Patients who met established criteria for preterm labor during their pregnancy were usually treated with parenteral magnesium sulfate or ritodrine hydrochloride at the discretion of the attending physician. Most women who received parenteral tocolytic therapy were also given oral β-sympathomimetic therapy after the intravenous medications were stopped. In the absence of contraindications, most of the patients in preterm labor received a course of tocolytic therapy. At our institution women are not prescribed parenteral tocolytic therapy after 35 completed weeks' gestation. Labor and delivery management decisions were made by the resident staff and attending physicians.

Data were analyzed with the SAS (Statistical Analysis System, Carey, N.C.) software release 6.03 for personal computers and release 5.18 for the IBM 3270 mainframe. The χ^2 test of proportions was used where appropriate, and stepwise, multiple logistic regression was performed with the Logist procedure.[11]

Results

Of the 7952 gravidas with singleton gestations, 244 (3.1%) were excluded because they had an indicated preterm delivery. These patients represented 27% of

- Identification of the pregnancy at risk for preterm labor
  - Risk scoring system
- Interventions to recognize the early prodrome of and prevent the occurrence of preterm labor
  - Antenatal evaluation and education
  - Bed rest
- Interventions to treat preterm labor
  - Tocolytic therapy
- Interventions to decrease the morbidity associated with preterm birth
  - Transfer to level III center
  - Infection surveillance and treatment
  - Agents to accelerate lung maturation
  - Labor and delivery management
- Neonatal interventions to minimize the sequelae of preterm birth
  - Level III nursery

Fig. 2. Percentage of preterm birth (PTB) by score group and parity.

Table II. Incidence of preterm delivery by risk group (%)

	PTB risk group		*VPTB risk group*		
	Low	*High*	*Low*	*High*	*No.*
All patients	7.1	16.4	1.6	4.7	7478
Nulliparous patients	7.4	10.1	1.9	3.4	3439
Multiparous patients	6.8	19.3	1.3	5.3	4039

PTB, Preterm birth (<37 weeks); *VPTB*, very preterm birth (<32 weeks).

the entire preterm birth population. In addition, 230 (2.9%) were excluded because of a fetal or neonatal anomaly. Of the remaining 7478 women, 3439 (46%) were nulliparous and 4039 (54%) were multiparous. Of this study group of 7478 women, 85% were assigned a low-risk score, and 15% were assigned a high-risk score. Of the multiparous women 19% received a high-risk score, whereas only 10% of the nulliparous women had a score ≥10. The racial composition of the study group was 28% white and 72% nonwhite; the mean age was 22 ± 5 years (range, 11 to 46).

The incidence of preterm birth and very preterm birth according to risk group is shown in Table II. Fig. 2 depicts the incidence of preterm birth and very preterm birth by risk score partitions and parity groups. Whereas the likelihood of a multiparous patient being delivered of a premature infant increased with advancing score group, the number of patients who attained high scores was small. Conversely, the relationship between score group and preterm delivery in the nulliparous population was not as pronounced, and only two patients attained scores ≥20; neither had a preterm birth.

Summary predictive values are shown in Tables III and IV and reflect comparisons between the high- and low-risk groups. The positive and negative predictive values were determined from the observed incidences of preterm birth and very preterm birth in our population. Whereas the overall sensitivity and positive predictive values of the scoring system were poor, the multiparous group had considerably higher values than those of the nulliparous group. The negative predictive values and specificities, as others[12] have shown, were good.

The results of the multiple logistic regression analyses are shown in Table V. Of the risk variables that were entered into the algorithm (18 for the nulliparous group and 24 for the multiparous group), few were selected as significant contributors to either a preterm birth or a very preterm birth. Note that several risk factors were excluded from the logistic models because of an insufficient number of nonzero values (Table I). A history of preterm delivery was the most significant factor identified in the multiparous group, and a low prepregnancy weight was the best predictor in the nulliparous patients. Moreover, there was little overlap in risk factors between the nulliparous and multiparous populations. For each of the significant risk factors, the logistic regression analyses confirmed the relationship between a higher risk score value and the chance of preterm birth and very preterm birth.

Although ethnic background was not one of the risk variables in the scoring system, other authors[3] have reported that black women have an increased risk of spontaneous preterm delivery compared with white women. To evaluate race as an independent risk factor we performed the logistic regression as above but included a variable designated as "white" or "nonwhite." Race did not emerge as a significant independent risk factor for either preterm birth or very preterm birth ($p > 0.05$).

Comment

In this study we analyzed data collected as part of the multicenter trial of preterm birth prevention funded by the March of Dimes, and the study represents the center that entered the largest number of patients into the clinical trial. The results of the intervention program were disappointing.[9] Therefore analysis of each of the variables used in the risk scoring system is indicated. Our results show that even with the

carefully controlled application of a scoring system based on a combination of historic and pregnancy-related events in a large population, the sensitivity and positive predictive values of the risk assignments were poor. Moreover, its use in nulliparous women was limited even further because of the effects of parity on the predictive values. We believe that this is primarily a result of the influence of a prior preterm birth on future reproductive performance. By definition, nulliparous women lack the single most predictive risk factor in the scoring system. Although the clinical usefulness of a risk scoring system has been confirmed in some populations,[5, 6, 8] other reports have not been confirmatory. Main[12] has summarized the results of seven studies that dealt with preterm birth prevention and reported generally poor sensitivities and positive predictive values.

Screening tests should have a high sensitivity to allow treatment of the most patients at risk. If the intervention were either costly or carried a significant risk to the patient, then a high positive predictive value would also be necessary. In this case the treatment, a formal program of prematurity prevention, appears to have few significant ill effects.[9] Conversely, such a program is costly for the system and perhaps to the individual patient (frequent visits), but this has not been fully evaluated.

As with others,[3] we excluded patients who underwent an indicated preterm birth because to include these patients might have made an unrealistic demand on a scoring system that was devised to predict spontaneous preterm birth. Conversely, certain factors such as chronic hypertension, extremes of maternal age, and cigarette smoking could be related to the development of pregnancy complications severe enough to prompt a preterm delivery. A possible explanation for this postulate is that the protocol of preterm birth prevention was not designed to treat this type of patient. To answer this question, one could include this group of patients in the analysis.

The decision to include only patients with a singleton gestation may have influenced our results inasmuch as the relationship between multiple gestation and preterm labor is well established. But, given the other well-recognized obstetric complications of a multiple gestation, we thought that the use of a scoring system to identify these patients was of little clinical value. Finally, we excluded patients who had an anomalous fetus. We could identify no risk factors, save advanced maternal age, that could have predicted this type of adverse pregnancy outcome and believe that this removed a possible source of bias from the analysis.

Multiple logistic regression analyses of the multiparous and nulliparous groups at both pre-32 and pre-37 week end points showed different sets of significant risk factors. The reason for this disparity is unclear. Although the nulliparous model was allowed six fewer risk variables by design, the multiparous model contained all the risk variables that had a sufficient number of nonzero values. Of these only a low prepregnancy weight and a history of preterm birth were significant at both gestational age end points for the nulliparous and multiparous patients, respectively. Other authors[3] initially used a univariate analysis to identify significant risk variables for inclusion in a logistic regression model. A univariate procedure that screens for variables used in a multiple logistic regression analysis may be blind to the interaction patterns among the parameters of interest. Therefore we performed the entire analysis with multiple logistic regression with a stepwise, backward elimination procedure. This method permitted the multivariate analysis of each variable adjusted for the others present in the model and ultimately selected risk factors that made a significant ($p \leq 0.05$) contribution to the prediction of spontaneous premature delivery.

Because the usefulness of a risk scoring system has been shown in other populations, we considered why it had such a poor positive predictive value in our patients. From a socioeconomic standpoint our patients were relatively homogeneous and represented an underprivileged group. Therefore risk variables chosen to stratify patients by their economic class, acknowl-

Table III. Summary predictive values for delivery <37 weeks

	Sensitivity	*Specificity*	*PV+*	*PV−*
All patients	0.29	0.86	0.16	0.93
Nulliparous patients	0:14	0.90	0.10	0.93
Multiparous patients	0.40	0.83	0.19	0.93

PV+, Positive predictive value; *PV−*, negative predictive value.

Table IV. Summary predictive values for delivery <32 weeks

	Sensitivity	*Specificity*	*PV+*	*PV−*
All patients	0.34	0.85	0.05	0.98
Nulliparous patients	0.17	0.90	0.03	0.98
Multiparous patients	0.49	0.82	0.05	0.99

PV+, Positive predictive value; *PV−*, negative predictive value.

Table V. Significant risk variables from logistic regression analysis

	Nulliparous patients		*Multiparous patients*	
Delivery before	*Variable*	*p Value*	*Variable*	*p Value*
37 weeks	Low prepregnancy weight	0.006	Prior preterm delivery	<0.001
	Poor weight gain	0.04	Prior cone biopsy	<0.001
	Education	0.04	Bleeding after 12 wk	<0.001
	Employment status	0.04	Maternal age	<0.001
			Marital status	0.02
32 weeks	Low prepregnancy weight	0.03	Prior preterm delivery	<0.001
			Cervix dilated at 22 wk	0.01
			Second-trimester losses	0.05
			First-trimester losses	0.01

edging the contribution of socioeconomic factors to preterm birth, would have been extraneous. Another consideration was the validity of historic data used in the scoring system. A negative response to questions about the presence of a uterine anomaly or in utero exposure to diethylstilbestrol must be viewed as problematic, because this information may not have been reliably ascertained in our population. Other factors, such as amniotic fluid volume disorders, depend on serial ultrasonographic information that may not have been obtained. Because our study participants were not blinded to the status of their risk group, it is conceivable that this knowledge somehow influenced the natural history of preterm birth. This possibility cannot be excluded without further research. A similar concept might also be applicable to our inclusion of the intervention group patients, despite the fact that no difference in the preterm birth rate was observed. Finally we considered that the content of our routine prenatal care and our use of tocolytic agents may have altered or masked the predictive values inherent in the risk scoring system. Nevertheless, despite its poor sensitivity and positive predictive value, the risk scoring system does identify a group of patients at significantly increased risk of preterm delivery. In the multiparous population, high-risk patients had nearly three times the incidence of preterm birth and four times the incidence of very preterm birth compared with low-risk patients.

We concur with Iams[13] that current risk scoring systems are flawed by a lack of information about the specific pathophysiologic events that initiate premature labor. On the other hand, can the knowledge gained by the study of these risk factors contribute to this critical area of research? Most important, can the use of a preterm birth prevention risk scoring system make a manifest contribution to prenatal care? Certainly the identification and correction of such factors as poor weight gain are desirable. Despite these possibilities, the clinical usefulness of this risk scoring system appears to be limited, and its dissemination into obstetric practice should await further proof of its efficacy.

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A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis

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We compared oral magnesium oxide with oral terbutaline sulfate in a prospective, randomized manner to determine efficacy and side effects. Preterm labor patients whose labor was arrested with parenteral tocolysis were randomized to oral tocolysis with either magnesium oxide, 200 mg every 3 to 4 hours ($n = 23$), or terbutaline, 2.5 to 5 mg every 3 to 4 hours ($n = 27$). The number of patients who were delivered of infants before 36 weeks' gestation was similar between groups (18.5% receiving terbutaline versus 17.4% receiving magnesium). At least one side effect occurred in 81.5% of patients in the terbutaline group and 47.8% in the magnesium group ($p < 0.01$). Finally, the cost for 1 day of magnesium (20 cents) is approximately one third the cost of terbutaline (56 cents). These data suggest that oral magnesium oxide is as effective as terbutaline for the maintenance of tocolysis, with fewer side effects and at a lower cost. (AM J OBSTET GYNECOL 1990;163:879-82.)

Key words: Preterm labor, tocolysis, oral magnesium, oral terbutaline

Patients with successfully arrested preterm labor are generally given oral tocolytic medication until pregnancy is judged to be near term. This oral tocolytic therapy is intended to decrease recurrences of preterm labor and increase the chances of term delivery. β-Sympathomimetic agents are currently the agents of choice for this therapy. However, patients treated with oral β-sympathomimetic agents frequently have unpleasant side effects. Some patients may even discontinue their medication because of the side effects.[1-3] Further, the cost of β-sympathomimetic agents may be prohibitive for some patients.

Recently, oral magnesium has been suggested to be an effective and economical alternative to β-sympathomimetic agents.[3-5] However, there have been no prospective; randomized studies that compare the two drugs. We sought to compare, in a prospective randomized fashion, oral magnesium oxide with oral terbutaline sulfate in the maintenance of tocolysis.

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Materials and methods

The study population consisted of 60 preterm labor patients who had labor successfully arrested with parenteral therapy. The study was approved by the Institutional Review Board at The University of Texas Health Science Center at San Antonio. Informed consent was obtained from all patients before entry to the study. The criteria for diagnosis of preterm labor were: (1) gestational age between 25 and 35 weeks as determined by last menstrual period and real-time ultrasonography; (2) three contractions in 20 minutes that persisted despite intravenous hydration with 500 ml of normal saline solution and prolonged sedation with 8 to 20 mg of morphine sulfate; (3) any cervical change.

Table I. Patient characteristics

	Terbutaline (n = 27)	*Magnesium (n = 23)*	*p Value*
Age (yr)	22.9 ± 5.8	24.1 ± 7.1	NS
Gravidity (median)	2.0	2.0	NS
Parity (median)	1.0	1.0	NS
Education level (yr) (median)	12	11	NS
Dilatation (cm)	0.5 ± 0.8	0.8 ± 1.2	NS
Effacement	20% ± 28	23% ± 32	NS
Station (median)	−3	−3	NS
Estimated gestational age on entry (wk)	31.3 ± 3.3	31.8 ± 2.1	NS

Table II. Pregnancy outcome data

	Terbutaline (n = 27)	*Magnesium (n = 23)*	*p Value*
Estimated gestational age at delivery (wk)	37.9 ± 2.4	38.3 ± 2.3	NS
Birth weight (gm)	3028 ± 438	2954 ± 513	NS
Before 36 wk estimated gestational age (%)	18.5	17.4	NS
Before 36 wk Dubowitz (%)	11.1	4.3	NS
Days on oral tocolytic agents	28.5 ± 23.1	26.7 ± 18.5	NS
Discontinued therapy (%)	11	9	NS
Cost per day	56 cents	20 cents	—

The choice of parenteral tocolytic agent was at the discretion of the resident physician in charge of the patient's care. After achieving uterine quiescence for 12 to 24 hours, the patients were randomized into one of the two oral tocolytic treatment groups. Group I received magnesium oxide, 200 mg orally every 3 to 4 hours. Patients assigned to Group II received 2.5 to 5 mg of terbutaline sulfate orally every 3 to 4 hours. For the first 24 hours of oral therapy, the patients were maintained on strict bed rest. Light ambulation was begun on the second day. If the patient showed no evidence of recurrent preterm labor, she was discharged at 48 to 72 hours.

Patients were evaluated for recurrent preterm labor during weekly clinic visits. They were questioned concerning side effects and compliance. Patients were specifically asked about experiencing a "fast heart rate," "feeling your heart beating in your chest," nervousness, shaking, nausea, vomiting, diarrhea, or any other symptoms. If a patient failed to attend clinic, she was contacted at home and information concerning side effects was elicited. The patients were maintained on oral tocolytic agents until 36 completed weeks' gestation. Patients who underwent recurrent preterm labor while taking oral tocolytic agents were restarted on parenteral therapy. If treatment was successful they were placed on the oral tocolytic agent to which they were originally randomized.

Statistical analysis was performed with the χ^2 test or the Fisher exact test for categoric variables. For continuous variables, the two-tailed Student t test was used and for interval variables the Wilcoxon rank-sum test was used. An α of <0.05 was considered significant.

Results

Sixty patients were enrolled in the study, with 31 patients in the terbutaline group and 29 in the magnesium group. Ten patients were lost to follow-up or withdrew from the study. Four of these were in the terbutaline group and six were in the magnesium group, resulting in 27 assigned to the terbutaline group and 23 to the magnesium group. As shown in Table I, patient characteristics on entry to the study were comparable between the two study groups. There was one set of twins in each study group.

Fig. 1 displays the difference in side effects between the two groups. Patients in the terbutaline group typically complained of palpitations, fast heart rate, shaking, and nervousness, whereas the magnesium group had diarrhea. Overall, 81.5% of patients in the terbutaline group complained of a least one side effect versus 47.8% in the magnesium group ($p < 0.01$). The number of patients who discontinued therapy because of side effects was not significantly different in the two groups. Pregnancy-outcome parameters were similar

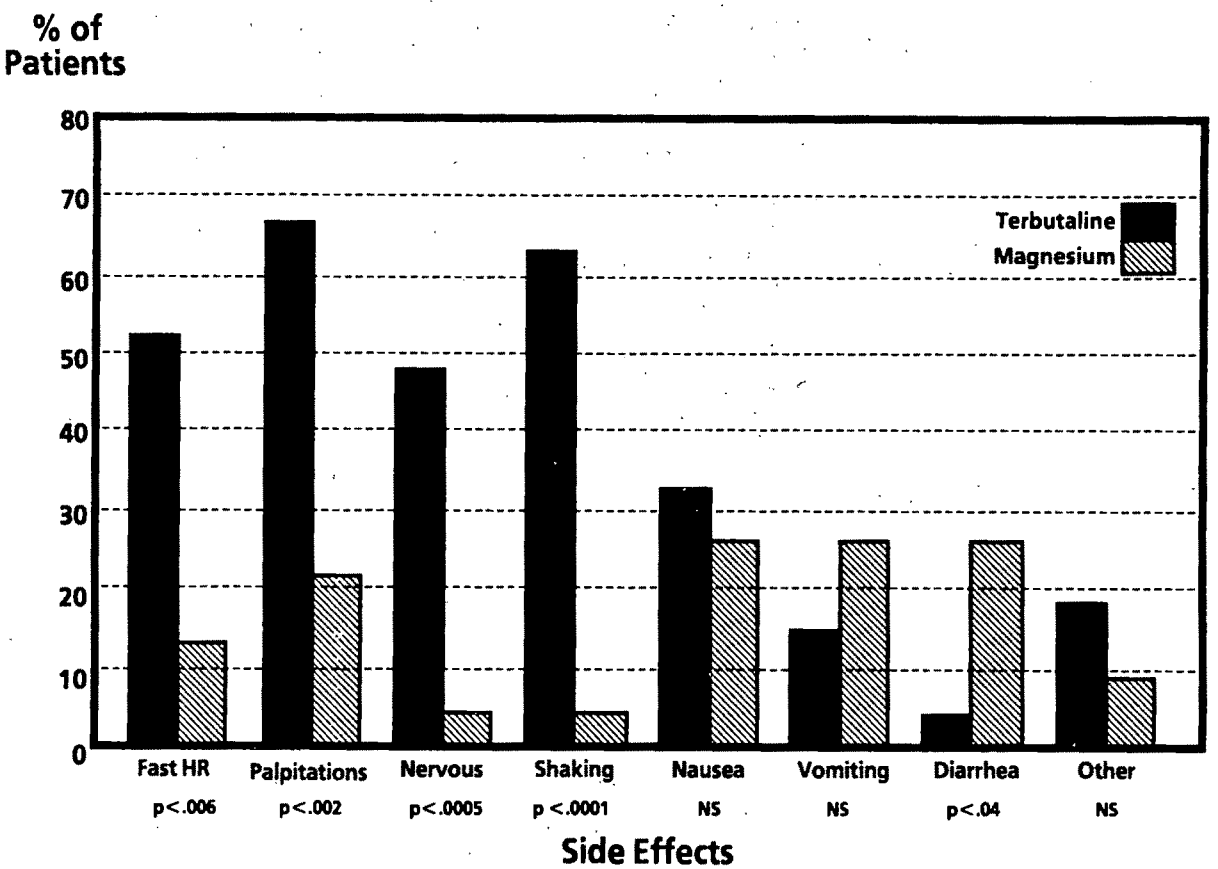


Fig. 1. Percentage of patients reporting side effect with oral terbutaline and oral magnesium oxide.

between groups; however, the daily cost of terbutaline is almost three times that of magnesium (Table II). Likewise, the number of recurrent preterm labor episodes between groups did not differ significantly. There were 11 episodes of recurrent preterm labor in eight patients in the terbutaline group and 13 episodes in eight patients in the magnesium group.

Comment

Our data suggest that oral magnesium oxide is as effective as oral terbutaline for the maintenance of tocolysis. Furthermore, side effects are less common and treatment is less costly when this drug is used.

Oral β-sympathomimetic agents have been shown to be useful in the maintenance of tocolysis. Creasy and associates showed that oral ritodrine significantly lengthened the time between start of oral therapy and first relapse of preterm labor. However, 50% of the patients in the ritodrine group complained of palpitations and flushing, whereas only 33% of the placebo group had similar complaints.[1] Brown and Tejani[2] showed that oral terbutaline, after tocolysis with ethanol, resulted in significantly more time gained in utero than did placebo. No control-group patient complained of palpitations, nervousness, restlessness, or nausea, whereas an average of 10% of the treatment group had at least one of these complaints.[2] Martin and others[3-5] have suggested that oral magnesium salts may be useful for oral maintenance of tocolysis. Martin et al.[3] compared oral ritodrine and magnesium gluconate in a prospective, non randomized manner and found as we did that oral magnesium was as effective as β-sympathomimetics in prolongation of pregnancy. These authors[3] found that 40% of the ritodrine group and 16% of the magnesium group complained of side effects. However, this was not significantly different and patients were not questioned about specific side effects.[3] With regard to efficacy, the power of our study and that of Martin[3] is admittedly low. We had a power of 0.50 to detect a 0.20 difference in the proportion of patients delivered of infants before 36 weeks' gestation.

The diagnosis of preterm labor in our study was made on the basis of the continuation of uterine contractions, despite hydration and sedation, accompanied by any cervical change. This resulted in a high rate (18%) of preterm delivery despite therapy. Our preterm delivery rate is comparable to that in Martin's study[3] (20%). Thus we showed the similar drug effi-

cacies of oral terbutaline and magnesium oxide. In contrast, a higher rate of side effects was found in patients treated with oral terbutaline versus oral magnesium oxide. Indeed, over 80% of the patients in the terbutaline group had at least one side effect. However, both our study and that of Martin[3] were unable to show an increased number of patients who discontinued therapy because of side effects. An additional consideration should be the cost of therapy. Comparison between the drugs reveals that the cost of 1 day of therapy with magnesium oxide (20 cents) is approximately one third the cost of 1 day of therapy with terbutaline (56 cents).

In summary, we believe that oral magnesium oxide is as effective as β-sympathomimetics for the maintenance of tocolysis. Furthermore, maintenance therapy is achieved with a lower incidence of side effects.

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Awaiting cervical change for the diagnosis of preterm labor does not compromise the efficacy of ritodrine tocolysis

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We retrospectively studied 209 patients treated with ritodrine hydrochloride to determine whether change in cervical effacement or dilatation during a period of observation before therapy would result in decreased efficacy of ritodrine, as measured by delivery delays of 48 hours, 1 week, or until ≥37 weeks' gestation; neonatal intensive care unit admission; and neonatal respiratory distress syndrome. Patients who were ≥3 cm dilated on admission were at high risk of therapy failure by all outcome measures compared with patients <3 cm dilated. For patients <3 cm dilated on admission, there was no difference in outcome when patients treated for contractions only were compared with those treated after change in effacement or dilatation had been documented. We conclude that awaiting change in cervical effacement or dilatation to be more certain of the diagnosis of preterm labor will not compromise the efficacy of ritodrine tocolysis. (AM J OBSTET GYNECOL 1990;163:882-6.)

Key words: Ritodrine hydrochloride, cervical effacement and dilatation, tocolytic efficacy

The diagnosis of preterm labor is traditionally made by documenting regular uterine contractions accompanied by progressive change in cervical effacement or dilatation during a period of observation.[1] However, when evaluating a patient possibly in preterm labor, clinicians are commonly concerned that awaiting cervical change to be certain of the diagnosis of preterm labor might compromise subsequent tocolytic efficacy.[2] Thus tocolytic medications are frequently administered on recognition of preterm uterine activity, before the documentation of cervical change. This management may result in the exposure of patients who are not in preterm labor to the potential risks of tocolytic medi-

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cations. Specifically, clinical experience with ritodrine hydrochloride has resulted in cardiovascular and metabolic toxicities, and maternal deaths have been associated with ridodrine therapy.[3-11]

Ideally, ritodrine would be used only in patients demonstrating "true" preterm labor. Whereas conservatism in administration of ritodrine must be weighed against the concern that awaiting cervical change will reduce tocolytic efficacy, no compelling evidence exists to support either that aggressive tocolysis enhances treatment success or that withholding treatment until cervical change occurs increases treatment failure. This study was undertaken to determine whether tocolysis instituted after documented change in cervical effacement or dilatation is less efficacious than tocolysis instituted only for uterine activity.

Material and methods

Parenteral ritodrine hydrochloride has been the primary pharmacologic treatment of preterm labor at Prentice Women's Hospital and Maternity Center. All patients treated with ritodrine between Jan. 1, 1985, and Dec. 31, 1988, were retrospectively identified. Excluded were patients with ruptured membranes before institution of ritrodrine, treatment before transfer to our institution, treatment with magnesium sulfate before ritodrine, or delivery elsewhere. These exclusions yielded 209 patients who were delivered of 237 infants.

Patients admitted with suspected preterm labor were initially observed for at least 1 hour with bed rest in the left lateral decubitus position, hydration (500 to 1000 ml of isotonic solution over 1 hour), and uterine contraction monitoring. Persistence of regular uterine contractions (all patients had regular uterine contractions at least every 10 minutes; 90% of patients had contractions at least every 5 to 6 minutes) was required for the diagnosis of preterm labor; awaiting change in cervical effacement or dilatation during the period of observation was encouraged but was not required. Whenever possible, serial cervical examinations were performed by a single examiner. Ritodrine was initiated by intravenous pump infusion at 0.10 mg/min and increased by 0.05 mg/min until the minimum dose that maintained uterine quiescence was achieved. After 6 to 12 hours of maintenance intravenous therapy, oral ritodrine hydrochloride was instituted and continued to 36 to 37 weeks' gestation.

Information obtained for each patient included age, race, clinic status (private versus service), prior pregnancy history and complications, medical history, and current pregnancy complications. Gestational age assignment was made on the basis of menstrual dates confirmed by ultrasonography or ultrasonographic age in the absence of a reliable menstrual history. Initial cervical examinations were documented, and any change in cervical effacement or dilatation that occurred before tocolysis was noted.

Table I. Distribution of patients by cervical examination

Admission cervical dilatation (cm)	*No cervical change before tocolysis (No.)*	*Dilatation or effacement before tocolysis (No.)*
0	29	29
>0 to <1	10	16
≥1 to <2	32	22
≥2 to <3	27	8
≥3	32	4

Patients were grouped according to cervical dilatation on admission and by the presence or absence of cervical change before initiation of tocolysis (Table I). Outcome data for the resulting groups were compared including gestational age at delivery; days gained after initial tocolysis; delivery delays of 48 hours, 1 week, or until ≥37 weeks' gestation; necessity of neonatal intensive care unit (NICU) admission; and neonatal respiratory distress syndrome (RDS). Maternal side effects and toxicities deemed significant enough to warrant a change in therapy by the examining physician were noted.

Continuous data were compared with the unmatched Student t test for two samples. Discrete data were investigated with χ^2 and the Fisher exact test where appropriate. Mantel-Haenszel χ^2 was used to detect confounding variables, and therapeutic end points were tested while controlling for confounding variables. A test of trends on the basis of odds ratios determined whether incremental degrees of cervical change after admission increased the risk of tocolytic failure. Trends were tested for significance by corrected χ^2. Stepwise multiple logistic regression tested obstetric, demographic, and historic variables for significant associations with our therapeutic end points. Delivery delays of 48 hours, 1 week, and until term; NICU admission; and RDS were analyzed as dependent variables. In all tests, p values <0.05 were considered statistically significant.

Results

Table II shows that, despite similar risk factors for preterm delivery, patients who were ≥3 cm dilated at admission ($n = 36$) were at significantly increased risk of adverse outcome compared with patients <3 cm dilated ($n = 173$). This occurred despite 89% (32/36) of patients in the ≥3 cm group being treated for contractions only before documented cervical change. Because of the significant risk of therapy failure in the patients ≥3 cm dilated, their inclusion strongly biases

Table II. Comparison of patients ≥3 cm versus <3 cm dilated on admission

	<3 cm (n = 173)	*≥3 cm (n = 36)*	*p Value*
Gestational age at admission (wk)*	30.7 ± 3.5	31.1 ± 3.2	NS
Multiple gestation	25 (14.5%)	3 (8.3%)	NS
Prior preterm delivery/parous patients	46/94 (48.9%)	12/27 (44.4%)	NS
Nonwhite	83 (48.0%)	15 (41.7%)	NS
Service patients	84 (48.6%)	16 (44.4%)	NS
Parous	94 (54.3%)	27 (75%)	<0.05
Maternal age (yr)*	28.2 ± 6.2	26.3 ± 7.1	NS
Gestational age at delivery (wk)*	36.0 ± 4.7	32.8 ± 4.0	<0.001
Days gained after tocolysis*	35 ± 28	12 ± 13	<0.001
48 hr delivery delay	156 (90.1%)	21 (58.3%)	<0.001
1 wk delivery delay	139 (80.3%)	19 (52.8%)	<0.001
Delivery ≥37 wk	76 (43.9%)	6 (16.7%)	<0.05
NICU admission	51/198 (25.8%)	22/39 (56.4%)	<0.001
Neonatal RDS	33/198 (16.7%)	13/39 (33.3%)	<0.05

*Mean ± 1 SD.

Table III. Comparison of patients with and without cervical change before tocolysis

	Group 1: No cervical change before tocolysis (n = 98)	*Group 2: Dilatation or effacement before tocolysis (n = 75)*	*p Value*
Gestational age at admission (wk)*	30.3 ± 3.8	31.2 ± 2.9	NS
Contraction frequency (min)*	4 ± 2	4 ± 2	NS
Dilatation at admission (cm)*	1.0 ± 0.8	1.2 ± 0.7	NS
Multiple gestation	13 (13.2%)	12 (16%)	NS
Prior preterm delivery/parous patients	25/52 (48.1%)	21/42 (50%)	NS
Nonwhite	51 (52.0%)	32 (42.7%)	NS
Service patients	40 (40.8%)	44 (58.7%)	<0.05
Parous	52 (53.1%)	42 (56.0%)	NS
Maternal age (yr)*	29.1 ± 5.8	27.1 ± 6.6	<0.05
Gestational age at delivery (wk)*	35.5 ± 4.0	36.6 ± 5.5	NS
Days gained after tocolysis*	36 ± 28	35 ± 29	NS
48 hr delivery delay	90 (91.8%)	67 (89.3%)	NS
1 wk delivery delay	76 (77.6%)	63 (84.0%)	NS
Delivery ≥37 wk	38 (38.8%)	38 (50.7%)	NS
NICU admission	28/111 (25.2%)	23/87 (26.4%)	NS
Neonatal RDS	18/111 (16.2%)	13/87 (14.9%)	NS

*Mean ± 1 SD.

the overall outcome in the group of patients treated before cervical change. To avoid this bias, the 36 patients ≥3 cm dilated on admission were excluded from subsequent analyses.

Of the remaining 173 patients, 98 had no cervical change before tocolysis (group 1), and 75 had documented change in cervical effacement or dilatation before tocolysis (group 2). As depicted in Table III, groups 1 and 2 were similar in gestational age, dilatation, uterine contraction frequency on admission, and risk factors for preterm delivery. Despite cervical change before therapy, group 2 revealed no difference in any outcome parameter compared with group 1. Mantel-Haenszel χ^2 analysis revealed that multiple gestation, clinic status, race, prior preterm delivery, and maternal age <20 years were potential confounding variables. After controlling for these variables there still were no differences in outcomes between group 1 to group 2.

By corrected χ^2 analysis the frequency of each outcome parameter was no different in the patient groups defined by either no change in effacement or dilatation before therapy or by incremental effacement or dilatation (effacement only; >0 but ≤1 or >1 but ≤2 cm dilatation change) before therapy. Likewise, a test of trends detected no increased risk of any adverse outcome with successive increments of cervical effacement or dilatation observed before initiation of tocolysis (Fig. 1).

Stepwise multiple logistic regression indicated that admission cervical dilatation of ≥2 to <3 cm was negatively associated with delivery delays of 48 hours, 1 week, and delivery at term, and positively associated with NICU admission and RDS. Admission dilatation of ≥1 to <2 cm was negatively associated with delivery at term. However, the presence of effacement or dilatation change before therapy, when added stepwise to the model, did not strengthen these associations. No other variables added singly or in combination were significantly associated with the outcomes tested. When evaluated as a single independent variable, cervical change before therapy was not associated with any of the therapeutic end points evaluated.

Because cervical dilatation of ≥2 to <3 cm on admission was associated with adverse outcome on logistic regression, the data were reanalyzed to compare outcome parameters in those with and without cervical change before therapy but <2 cm dilated on admission. The results were unchanged.

A tocolytic side effect or toxicity that prompted a change in therapy was documented in 31 cases (15%). Chest pain, tachycardia, and dyspnea that resolved with reduction or discontinuation of the ritodrine infusion were the most frequent side effects (n = 26), but

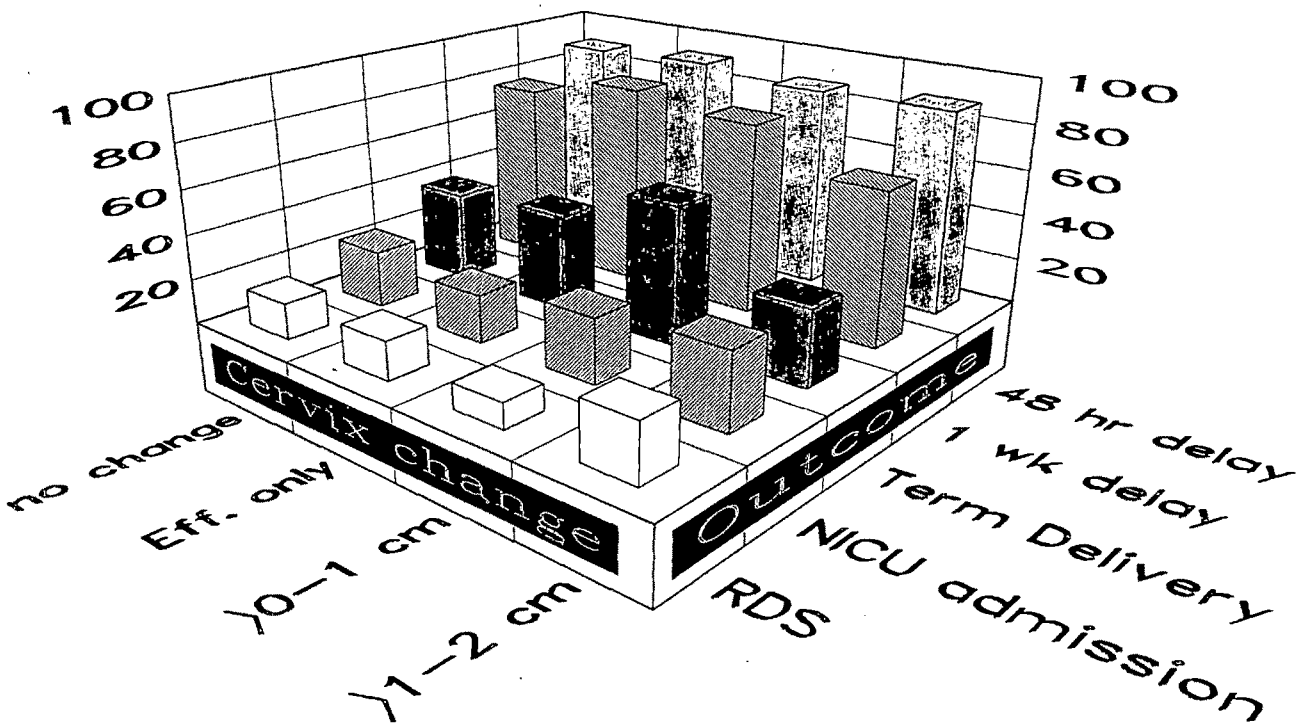


Fig. 1. Influence of incremental changes in effacement (*Eff*) or dilatation before tocolysis on frequency of pregnancy outcomes (measured as precentage of patients in each group).

pulmonary edema developed in two patients during therapy.

Comment

It is a commonly held opinion that by the time cervical change has been documented it is frequently too late to inhibit preterm labor.[2] This concern motivates physicians to administer ritodrine immediately on documentation of preterm uterine contractions, before documentation of cervical change. However, the effectiveness of ritodrine therapy in the prevention of preterm delivery is controversial. Despite the approval of ritodrine for treatment of preterm labor in 1980, a decrease in the overall prevalence of preterm birth has not been documented.[12] In addition, a meta-analysis of randomized placebo-controlled ritodrine trials by King et al.[13] suggested that ritodrine is somewhat effective in the delay of delivery but not in the prevention of neonatal RDS or death.

The diagnosis of preterm labor is often equivocal. In the 12 trials in King's meta-analysis, a range of 38% to 100% of the controls continued pregnancy for 24 hours; 27% to 89% continued pregnancy for 48 hours; and up to 54% were delivered of infants at term. Uterine activity was necessary for the diagnosis of preterm labor in all studies, and most required some degree of cervical dilatation. Even with cervical dilatation present, either many patients were not in preterm labor, or bed rest alone was an effective treatment for preterm labor. Preterm contractions without documented change in cervical effacement or dilatation would seemingly make the diagnosis of preterm labor even less certain. Despite common concern that cervical change may compromise tocolytic efficacy, to our knowledge this is the first study that objectively addresses this issue.

Our initial analyses revealed that, in contrast to patients with lesser degrees of dilatation, those who presented ≥3 cm dilated were at significant risk of failed tocolysis. Because almost all these patients were treated before documented change in effacement or dilatation, we were unable to evaluate the influence of further cervical change on tocolytic efficacy. However, the high risk of failure after standard tocolytic therapy in this group suggests that patients first seen with preterm labor and advanced dilatation may be ideal candidates for investigation of alternative tocolytic regimens.

A potential for bias exists in any retrospective analysis. The most likely bias in this study would have been toward overtreatment of patients thought to be in preterm labor before documented cervical change (i.e. that some patients in group 1 were not truly in preterm labor). However, this would have tended to show a

much better outcome in group 1 compared with group 2. In fact, this was not the case. Thus our results support equal effectiveness of ritodrine therapy instituted after change in cervical effacement or dilatation compared with therapy instituted without cervical change for those patients first seen <3 cm dilated. Furthermore, our success rate of 89% in the delay of delivery for 48 hours and 50% in the delay of delivery until term in patients who had cervical change before therapy is similar to previously reported success rates.[7] The side effects and toxicities documented in this study and elsewhere underscore the potential risks of ritodrine therapy. These observations suggest that if rationalized only by a presumption of improved efficacy, institution of tocolysis before documented change in effacement or dilatation may not be warranted.

In conclusion, the results of this study show that hydration, rest, and observation is a safe alternative to immediate ritodrine tocolysis for patients who are <3 cm dilated when first seen. If uterine contractions persist and result in cervical change, ritodrine may still be effective.

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Gram stain results from amniocentesis in patients with preterm premature rupture of membranes—Comparison of maternal and fetal characteristics

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A total of 108 patients with preterm premature rupture of membranes who had undergone amniocentesis were retrospecively analyzed. Seventy-seven patients had negative amniotic fluid Gram stains and were managed expectantly. Thirty-one patients had positive amniotic fluid Gram stains confirmed by subsequent cultures and were delivered of infants on that basis. A univariate comparison of various parameters revealed significant differences in maternal temperature, pulse, and white blood cell count. Patients with positive Gram stains had lower mean gestational age, higher baseline fetal heart rate, and nonreactive fetal heart rate tracings. On the basis of a multivariate stepwise discriminate analysis, fetal heart rate >150 beats/min or nonreactive nonstress test were the best predictors of the Gram stain findings, with a sensitivity of 71%, specificity of 76%, and negative predictive value of 87%. These data suggest that in patients with preterm premature rupture of membranes and fetal tachycardia or nonreactive nonstress test, amniocentesis should be performed in the initial evaluation. (Am J Obstet Gynecol 1990;163:887-9.)

Key words: Premature rupture of membranes, Gram stain, fetal tachycardia, nonreactive nonstress test, infection

Rupture of membranes in preterm gestation remains a major contributor to perinatal morbidity and mortality as a result of complications of prematurity and sepsis.[1] The management of these patients has focused on identification of potentially infected fetuses and adjustment of management decisions on the basis of the results of diagnostic amniocentesis and ultrasonography.[2-9] This retrospective study compares maternal and fetal characteristics in patients with preterm premature rupture of membranes (PROM) and negative amniotic fluid Gram stains with patients with preterm PROM and positive amniotic fluid Gram stains to identify those characteristics that could be incorporated in a statistical model that would be predictive of Gram stain findings.

Material and methods

Charts of patients admitted to Long Beach Memorial Women's Hospital between 1984 and 1988 for preterm PROM and who had amniocentesis were reviewed. Only singleton pregnancies from 24 to 36 weeks' gestation not in labor on admission were included in the study. Patients with chorioamnionitis, bleeding, fetal distress, and those who had received antibiotics, glucocorticoids, or β-sympathomimetic agents were excluded.

Rupture of membranes was documented by sterile speculum examination with pooled fluid, ferning, and nitrazine paper determination. Electronic fetal monitoring was used to establish the presence of fetal distress and document uterine activity. Ultrasonographic evaluation was used in the assessment of gestational age and performance of amniocentesis. Amniotic fluid was sent for fetal lung maturity studies, Gram stain, and aerobic and anaerobic cultures. Patients with mature lung profiles were delivered of infants by oxytocin induction or by cesarean section if obstetrically indicated. Patients with positive Gram stains were begun on parenteral antibiotics and delivered of infants. Patients with negative amniotic fluid Gram stains and immature lung profiles were managed expectantly with daily nonstress test (NST) surveillance as described previously.[10]

Statistical analyses were made with the pooled Student *t* test and the Fisher exact test where applicable. A multivariate stepwise discriminate analysis was done with BMDP-7 statistical software (Regents University of California, Berkley, Calif., 1988). And α level of 0.05 was considered significant. All tests were made against a two alternative sided hypothesis.

Results

A total of 108 patients met with the study criteria and were included in the analysis. Seventy-seven patients

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6/6/22589

Table I. Univariate comparisons of maternal and fetal characteristics

*Gram stain characteristics**	*Negative (n = 77)*		*Positive (n = 31)*		*p Value*
	Mean	*SD*	*Mean*	*SD*	
Maternal age (yr)	26.8	5.8	26.0	4.9	NS
Gravity	3.1	2.1	3.8	2.0	NS
Parity	1.1	1.2	1.2	1.0	NS
Temperature†	36.9	0.4	37.3	0.7	0.0005
Systolic blood pressure	112.4	20.7	106.5	15.4	NS
Diastolic blood pressure	63.2	10.8	59.9	9.9	NS
Pulse	87.4	13.4	93.2	14.0	0.044
White blood cells	10.8	2.8	12.5	3.6	0.011
Gestational age (wk)	32.4	1.9	30.5	3.7	0.001
Latency (hr)‡	15.5	18.2	15.7	17.0	NS
Baseline heart rate	138.0	9.0	151.0	12.0	0.0005
NST					
Reactive§	—	$n = 77$	—	$n = 22$	0.000005
Nonreactive	—	$n = 0$	—	$n = 9$	0.000005

*Taken within 1 hour of the amniocentesis.
†Degrees Centigrade.
‡Latency period from time of PROM to amniocentesis.
§Acceleration of ≥15 beats/min for ≥15 seconds.

Table II. Predictive value of FHR > 150 and nonreactive NST

	Sensitivity (%)	*Specificity (%)*	*Predictive value*	
			Positive (%)	*Negative (%)*
FHR > 150	68	77	54	86
Nonreactive NST	29	100	100	78
FHR > 150 or nonreactive NST	71	76	55	87

had negative amniotic fluid Gram stains and were managed as outlined above. Thirty-one patients had positive amniotic fluid Gram stains and cultures and were delivered of infants on the basis of the Gram stain results.

Univariate comparisons of certain maternal and fetal characteristics were made as shown in Table I. All parameters were obtained within 1 hour of the amniocentesis. There were significant differences in maternal temperature, pulse, and white blood cell count ($p < 0.0005$, $p < 0.044$, and $p < 0.011$, respectively) between patients with negative and positive Gram stains. Patients with positive Gram stains had a lower mean gestational age, higher baseline fetal heart rate (FHR), and higher incidence of nonreactive FHR tracings ($p < 0.001$, $p < 0.0005$, and $p < 0.000005$, respectively). A multivariate stepwise discriminate analysis was performed. The two variables with the best predictive value of Gram stain results were FHR >150 beats and nonreactive NST (Table II) (F statistical value $2102 = 25.3$, $p < 0.0005$). On the basis of the results of the discriminate analysis, the sensitivity, specificity, and positive and negative predictive values of elevated baseline FHR or nonreactive NST were calculated (Table II).

Comment

A tremendous divergence of opinion exists concerning the proper management of rupture of membranes remote from term. Several authors have advocated the use of amniocentesis in patients with preterm PROM to assess both pulmonary maturity and the microbiologic status of amniotic fluid.[2,3,8,9] This approach identifies and allows for expectant management of the noninfected patient. More recently Vintzileos et al.[4,6,7] and Goldstein et al.,[5] proposed the use of the biophysical profile in the management of these patients, predicated on the assumption that fetuses within a noninfected amniotic cavity behave differently from fetuses exposed to intraamniotic infections. These studies showed that fetuses in an infected environment have lower overall biophysical profiles, with decreased fetal breathing and movements. The present analysis supports these reports in that fetuses that reside in a colonized milieu will often manifest characteristics that are different from fetuses in an uninfected amnioitic cavity. In the present study the patients with positive Gram stains and culture had a significantly lower gestational age than that of those with negative Gram stains (30.5 weeks versus 32.4 weeks). Whereas it is true that there is a

maturational process that occurs in the baseline FHR and FHR acceleration with advancing gestational age, the difference in mean gestational age of 1.9 weeks seen between the gram-positive and gram-negative groups is not great enough to account for the statistically significant difference in FHR reactivity and baseline heart rate observed between the two groups.[11]

Because amniocentesis is invasive and difficult to perform in patients with PROM (especially those with very low fluid volume), many clinicians do not include amniotic fluid Gram stain and culture in the routine assessment of patients with preterm PROM. The diagnosis of early or subclinical chorioamnionitis, although desirable, is difficult in the absence of fever. Symptoms such as leukocytosis are quite nonspecific. The data presented here would support that the presence of fetal tachycardia (FHR > 150 beats/min) and nonreactive FHR tracing is highly suggestive of occult intraamniotic infection, and that amniocentesis to verify this suspicion is warranted.

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Adjusting the loading dose of magnesium sulfate for tocolysis

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The purpose of this prospective study was to establish a method to calculate a loading dose of magnesium sulfate so as to achieve therapeutic levels of tocolysis more quickly. Fifty patients in preterm labor were enrolled. In the first phase 25 patients were studied so that the apparent volume of distribution for the loading dose of magnesium sulfate could be estimated and an adjusted loading dose could be calculated. The efficacy of this adjusted loading dose was then tested on a further 25 patients in the second phase. We found that the apparent volume of distribution could be accurately estimated and an adjusted loading dose calculated, with the use of ideal body weight, degree of underweight, and current use of β-sympathomimetics. In the adjusted loading dose group therapeutic levels were achieved more often, with higher postloading magnesium levels and a greater decrease in contraction index immediately after the loading dose. We conclude that an adjusted loading dose can be calculated for magnesium sulfate to optimize tocolytic therapy. (AM J OBSTET GYNECOL 1990;163:889-92.)

Key words: Magnesium, magnesium dosage, tocolytics, magnesium pharmacology

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Magnesium sulfate is a commonly used parenteral tocolytic. It has been shown to be as effective as β-sympathomimetics with a lower incidence of serious side effects.[1-3] However, a longer period of time is required to achieve uterine quiescence with magnesium than with β-sympathomimetics.[1]

Several studies have demonstrated a need to achieve

Table I. Ideal weight table

Height*	Ideal weight† (kg)		
	Small frame	*Medium frame*	*Large frame*
4'11"	49.8	54.3	58.9
5'0"	50.9	55.5	60.2
5'1"	52	56.8	61.6
5'2"	53.4	58.2	63.2
5'3"	54.8	59.5	64.8
5'4"	56.1	60.9	66.4
5'5"	57.5	62.3	68.0
5'6"	58.9	63.6	69.5
5'7"	60.2	65	70.7
5'8"	61.6	66.4	72.5

Modified from 1983 Metropolitan life table.
*Height without shoes.
†Weight in patient gown.

a minimum therapeutic concentration of magnesium ions to suppress uterine activity.[1, 4-6] However, these levels are rarely achieved with the typical 4 gm loading dose of magnesium sulfate.[5] To achieve a therapeutic level of magnesium while avoiding potential toxicity, knowledge of the volume of distribution of magnesium is needed. However, no previous studies address the issue of the volume of distribution for the loading dose of magnesium sulfate in patients in preterm labor.

The goal of this study was to establish the apparent volume of distribution of the loading dose of magnesium sulfate so that an adjusted loading dose could be calculated and to investigate the efficacy of this adjusted loading dose.

Material and methods

In this prospective study, 50 patients admitted to the labor and delivery unit with preterm labor were enrolled. Preterm labor was defined as a gestational age of 24 to 35 weeks and regular uterine contractions accompanied by documented cervical change. Choice of tocolytic agent was by individual physician preference. In general, magnesium is used in our institution as the first-line drug for tocolysis. Patients with preexistent renal disease, suspected dehydration, or a contraindication to tocolysis were excluded.

The study was done in two phases with 25 patients in each phase. In phase I patients were given a 4 gm loading dose of magnesium sulfate ($MgSO_4 \cdot 7H_2O$ United States Pharmacopeia) infused intravenously over 15 minutes with an infusion pump. Blood samples for serum magnesium determination were drawn immediately before and 1 minute after the loading dose was given. Magnesium levels were determined by means of the calmagite reaction and a Paramax System (Baxter Scientific, Irvine, Calif.). Apparent volume of distribution (AVOD) was calculated by the equation: AVOD = $MgSO_4$ loading dose [grams] $\times 98$ [milligrams Mg++ per gram $MgSO_4$ / (Postloading level − preloading level [milligrams per deciliter]) $\times 100$ ml/dl. This formula reduced to: AVOD = 39,200/(Postloading level-Preloading level). Because patients in preterm labor often receive significant volumes of intravenous fluids before tocolysis AVOD was corrected by the following equation: True AVOD = Measured AVOD − (Intravenous fluids − Urine output).

For each patient, height, weight, ideal body weight, degree of weight over or under the ideal, gestational age, body surface area, presence of multiple gestation, previous exposure to magnesium, and current therapy with β-sympathomimetic tocolytics were recorded. Ideal body weight was estimated by a modified 1983 Metropolitan life table. This table was generated by taking the midpoint of the range of ideal weight for a given height and frame size, converting it to kilograms, and correcting for lack of shoes and clothing (Table I). For overweight patients, overweight was calculated by: Overweight = Actual weight − Ideal weight. For underweight patients underweight was calculated by: Underweight = Ideal weight − Actual weight.

Contraction monitor strips for 30 minutes before the loading dose began and 30 minutes after completion were photocopied for future analysis. After completion of the study, two blinded examiners scored the monitor strips for contraction index and number of contractions in 30 minutes. The contraction index was calculated as the total duration of contractions during 30 minutes of monitoring.

Stepwise linear regression was used to establish the relationship between apparent volume of distribution and the independent variables weight, ideal weight, underweight, overweight, body surface area, multiple gestation, previous exposure to magnesium, and current therapy with β-sympathomimetics.

In phase 2, apparent volume of distribution was estimated by the equation established in phase 1: AVOD = 613.1 + 215.7 (Ideal weight in kilograms) + 408.3 (Underweight in kilograms) − 2182.7 (if receiving β-sympathomimetic). The adjusted loading dose was calculated by this equation: Loading dose = AVOD [milliliters] × 5.2 [Expected change in serum Mg++] / (98 [milligrams Mg++ per gram $MgSO_4$] × 100 [milligrams per deciliter]). The simplified equations are shown in Table II. We assumed an approximate baseline level of 1.8 mg/dl and target level of 7 mg/dl. The minimum therapeutic level was defined as 6 mg/dl. Magnesium infusion technique, as well as other treatment and data collection, was identical to that of phase 1.

After phase 2 was completed, stepwise linear regression was again performed with study phase added as

Table II. Calculation of the adjusted loading dose

Apparent volume of distribution = 613.1 + 215.7 (Ideal weight, kilograms) + 408.3 (Underweight, kilograms) − 2182.7 [If receiving β-sympathomimetic]
Adjusted loading dose [grams] = 0.00053 × Apparent volume of distribution

*Appropriate safety precautions should be observed during magnesium infusion.

an independent variable. This was done to control for possible effects of higher loading doses on apparent volume of distribution.

Comparison of the groups was done by Student's t test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Stepwise linear regression was performed with the use of the variables as described above. Both forward and backward stepping procedures were used and generated identical methods. A BMDP statistical package was used for all statistical analysis with α of <0.05 considered significant.

Results

Patient characteristics were similar between the two groups with two exceptions (Table III). There were more underweight patients in phase 1 and a tendency toward use of magnesium as a first-line tocolytic in phase 2.

Stepwise linear regression of phase 1 data revealed that previous magnesium exposure, multiple gestation, actual weight, body surface area, or overweight had no effect on AVOD. The significant predictive variables were ideal weight (kilograms), underweight (kilograms), and current therapy with β-sympathomimetics related by the equation: AVOD = 613.1 + 215.7 (Ideal weight) + 408.3 (Underweight) − 2182.7 (if receiving β-sympathomimetic), $r = 0.61$, $p = 0.04$. Ideal weight from the modified 1983 Metropolitan life table was the best predictive factor. Furthermore, the negative regression coefficient for current therapy with β-sympathomimetics indicates that patients being treated with β-sympathomimetics had lower apparent volumes of distribution ($p = 0.045$).

Baseline magnesium levels and apparent volume of distribution were similar between phases. Postloading magnesium levels were significantly higher in phase 2 ($p < 0.001$) (Table IV).

As shown in Table V, the ability of the regression equation to choose an adjusted loading dose was demonstrated by a greater number of phase 2 patients who were above the therapeutic minimum level ($p = < 0.001$). Further, there was a greater decrease in contraction index ($p = 0.01$), suggesting improved

Table III. Patient characteristics

	Phase 1 (n = 25)	*Phase 2 (n = 25)*	*p Value*
Gestational age (wk)	31.0 ± 2.6	31.2 ± 2.8	NS
Weight (kg)	63.0 ± 14.6	68.7 ± 16.0	NS
Height (cm)	159.2 ± 5.1	158.3 ± 6.3	NS
Ideal body weight (kg)	57.4 ± 4.2	57.1 ± 4.6	NS
Underweight (kg)	2.1 ± 3.2	0.44 ± 1.1	0.02
Overweight (kg)	7.7 ± 11.4	11.9 ± 12.8	NS
Multiple gestation	3	3	NS
Previous magnesium sulfate	3	5	NS
Current β-sympathomimetics	9	2	0.04

Table IV. Apparent volume of distribution and magnesium levels by group

	Phase 1 (n = 25)	*Phase 2 (n = 25)*	*p Value*
Apparent volume of distribution (ml)	13067 ± 2911	12192 ± 2895	NS
Serum magnesium (mg/dl)			
Prepose	1.8 ± 0.3	1.9 ± 0.21	NS
Postdose	4.9 ± 0.81	7.5 ± 1.2	<0.001
Loading dose (gm)	4.0 ± 0	6.88 ± 0.79	—

tocolytic effects with the adjusted loading dose. The correlation between observers was 0.78 for contraction index and 0.88 for contractions per 30 minutes. Although more patients in phase 2 had successful delay of delivery for 48 hours, this did not reach significance.

Most patients in both phases experienced cutaneous flushing during infusion of the loading dose. Two patients in each group had severe nausea and vomited. No signs of magnesium toxicity, including loss of patellar reflexes, were seen. In addition, no serious side effects, such as pulmonary edema, were encountered in either phase.

Comment

We found that the apparent volume of distribution for magnesium can be estimated with clinical parameters. With this information we were able to calculate an adjusted loading dose of magnesium sulfate to achieve therapeutic levels quickly in most patients. Furthermore, this adjusted loading dose had a greater effect on contraction index in the immediate postloading period.

As expected, ideal body weight was the most powerful predictor of apparent volume of distribution. After establishing the regression equation to predict apparent volume of distribution, we attempted to use alternative

Table V. Effects of loading dose

	Phase 1 (n = 25)	*Phase 2 (n = 25)*	*p Value*
Postdose therapeutic level	3	23	<0.001
Contraction index			
Preloading	7.79 ± 2.65	7.98 ± 2.14	NS
Postloading	4.91 ± 2.64	3.27 ± 1.80	0.01
Mean % decrease	35.28 ± 35.57	57.71 ± 24.42	0.01
Contractions per 30 min			
Preloading	9.98 ± 5.67	9.11 ± 3.43	NS
Postloading	5.81 ± 4.22	4.07 ± 2.34	NS
Mean % decrease	37.62 ± 39.1	52.33 ± 29.11	NS
Delivery delayed 48 hr	20	23	NS

methods to estimate ideal body weight. These included the equation Ideal weight = 100 lb + 5 lb per inch of height greater than 5 feet, as well as corrections for pregnancy weight gain. None of these was as effective as the modified 1983 Metropolitan life table.

Interestingly, our regression model of apparent volume of distribution indicates that patients being treated with β-sympathomimetic tocolytics have a lower apparent volume of distribution for magnesium. Eleven of the patients in our study were being treated with β-sympathomimetics. Medication was changed to magnesium sulfate when the β-sympathomimetic agent failed to achieve tocolysis. β-Sympathomimetic tocolytics are usually associated with increased intravascular volumes.[7] However, magnesium is distributed far beyond the intravascular space, as indicated by an average apparent volume of distribution of 12.6 L. It is possible that β-sympathomimetics interfere with the entry of magnesium into cells and thus reduce total apparent volume of distribution.

A tendency toward use of magnesium sulfate as the initial tocolytic was seen in phase 2. Although that may bias the results concerning effects on contractions, apparent volume of distribution should not be affected, as current β-sympathomimetic therapy and phase of study were both used as independent variables during regression modeling. The slight tendency toward underweight patients in phase 1 seems to be a chance occurrence.

We excluded patients with renal disease or suspected dehydration because such patients may have lower apparent volumes of distribution resulting in excessively high postloading magnesium levels. None of the study patients experienced loss of patellar reflexes or other signs of magnesium toxicity. However, the potential for toxicity exists with any infusion of magnesium. Thus we recommend appropriate safety precautions be taken when an adjusted loading dose is used.

Several investigators have suggested the need to achieve a minimum serum level of magnesium to produce tocolysis. Harbert el at.[4] have shown that magnesium, at levels of 6 to 8 mEq/L (7.2 to 9.4 mg/dl), reduced uterine activity in monkeys, patients with preeclampsia and isloated myometrial strips. In a clinical study of preterm labor Elliott[5] found that levels of 5 to 7 mg/dl were effective for tocolysis. Hollander et al.[1] found the mean serum level to achieve tocolysis was 6.6 mg/dl. This group was a target serum magnesium concentration of 6 to 8 mg/dl. In a review of tocolytic agents, Caritis et al.[6] state that the labor-inhibiting level is 5.5 to 7.5 mg/dl. Our data demonstrate a greater reduction in contraction index with higher postloading magnesium levels. This suggests that quickly achieving a therapeutic magnesium level is desirable.

Some authors[6] have suggested using a 6 gm magnesium sulfate loading dose. Twenty-four of 25 patients in phase 2 received an adjusted loading dose of > 6 gm. Using apparent volumes of distribution obtained in phase 2, we estimate that only 19 of 25 patients would have achieved a level above 6 mg/dl after a 6 gm loading dose. Thus it seems that a loading dose of 6 gm would be better than 4 gm in most patients. However, using a 6 gm dose in a small patient who is receiving β-sympathomimetics may place that patient at high risk for toxicity. Therefore an adjusted loading dose technique may offer a balance of safety and efficacy.

Magnesium has been demonstrated to be equally as efficacious and to have fewer side effects than do β-sympathomimetics.[1-3] However, there is difficulty in achieving tocolysis quickly. This delay in tocolysis may be related to a delay in achieving therapeutic levels. Our data suggest that loading doses can be calculated for each patient in preterm labor to achieve therapeutic serum levels almost immediately. Further study is needed to determine the safety of this adjusted loading dose and whether it will improve the success of tocolytic therapy.

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Infants of diabetic mothers with accelerated fetal growth by ultrasonography: Are they all alike?

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We studied longitudinal ultrasonographic growth patterns (abdominal circumference, biparietal diameter) initiated early in gestation in 52 pregnancies complicated by pregestational diabetes mellitus and 19 controls. Three predominant patterns of growth were ascertained including a heretofore unrecognized pattern characterized by accelerated abdominal circumference growth (>90th percentile) before 24 weeks' gestational age. Maternal and neonatal anthropometric and metabolic parameters were contrasted for the three patterns. The findings suggest that in some cases of diabetic macrosomia that can be recognized before 24 weeks' gestation, augmented growth may be influenced by factors other than fetal hyperinsulinism. (AM J OBSTET GYNECOL 1990;163:893-7.)

Key words: Evolving macrosomia, diabetes mellitus, amniotic fluid insulin

Macrosomia has long been considered the hallmark of diabetic fetopathy. The Pedersen hypothesis[1] proposed nearly four decades ago links fetal hyperinsulinism induced by altered maternal metabolism to accelerated fetal growth and resultant macrosomia. Although macrosomia has traditionally been defined on the basis of birth weight, it has long been recognized that the infant of a diabetic mother typically has a disproportionate increase in such insulin-sensitive tissue as adipose, liver, and muscle but not in tissue such as bone, skull, and brain in which growth is relatively insulin insensitive.[2, 3] Accordingly, evolving macrosomia in utero has been detected by accelerated fetal abdominal circumference growth, a measurement that reflects insulin-sensitive tissue.[4-6]

Whereas there is experimental evidence in support of this pathophysiologic sequence, there has been limited reported success in the prediction of macrosomic fetal growth on an individual basis from conventional measure of maternal metabolic control. Whether this is a result of variability in the response of an individual fetus to its maternal metabolic milieu, limitations in the conventional tools used to assess metabolic effects on the fetus, or other reasons is not clear. Our objective was to examine whether all macrosomic infants of diabetic mothers conform to the same pattern of accelerated fetal growth and whether this pattern reflected measures of maternal metabolic control and fetal hyperinsulinism.

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Material and methods

A group of 52 pregestational insulin-dependent patients enrolled in the Diabetes in Pregnancy Center of Northwestern University between September 1977 to April 1983 met the following criteria: (1) two or more ultrasonographic examinations including both abdominal circumference (AC) and biparietal diameter (BPD) measurements, one ≤24 weeks' gestation (AC_1, BPD_1) and one ≥32 weeks' gestation (AC_2, BPD_2) gestation; (2) gestational age at delivery of ≥36 weeks' gestation. Nineteen women with normal carbohydrate metabolism as documented by the 3-hour oral glucose tolerance test according to the criteria of O'Sullivan and Mahan[7] and who exhibited normal ultrasonographic growth throughout pregnancy were included as controls. Each BPD measurement was made at the level of the thalami and the AC measurement was made at the level of the umbilical vein in the fetal liver. Growth percentiles were determined by plotting the individual measurements on growth charts derived from pregnancies at the same institution.[8]

Fasting plasma glucose values were drawn at each outpatient visit and at least twice weekly during hospitalization, and analyzed by the glucose oxidase method. With one exception all diabetic patients were hospitalized at least twice during pregnancy, once at enrollment and a terminal admission before delivery. Hemoglobin A_{1c} was measured monthly with column

Table I. Classification of ultrasonographic patterns of infants of diabetic mothers on the basis of abdominal circumference percentile

AC_2:	<10	10-90	>90
AC_1			
<10	0	1	0
10-90	2	17 (I)*	17 (II)*
>90	1	1	13 (III)*

AC_1, <24 weeks' gestation; AC_2, >32 weeks' gestation.

*Designated study group growth patterns: normal growth (I), late accelerated growth (II), and early accelerated growth (III).

chromatography.[9] Mean values for hemoglobin A_{1c} were derived for individual subjects by averaging all measurements obtained during each trimester. Mean values for fasting plasma glucose were calculated for each trimester from all outpatient values and from two values each week drawn on predetermined days during hospitalization. An overall pregnancy mean (mean of trimester means) was also derived for each patient. Patients underwent amniocentesis to evaluate fetal lung maturity at 34 to 38 weeks' gestation. Amniotic fluid insulin was measured by double antibody immunoassay and amniotic fluid glucose was measured by a glucose oxidase method.[10-12] If a patient had more than one amniocentesis, the maximum amniotic fluid insulin and amniotic fluid insulin/glucose ratio was used. Control patients underwent similar metabolic evaluation excluding amniocentesis and first-trimester fasting plasma glucose and hemoglobin A_{1c} measurements. All protocols were approved by the Institutional Review Board, and appropriate patient consents were obtained.

The following anthropometric variables were examined: maternal height and prepregnancy percent ideal body weight, neonatal birth length, birth weight, and birth symmetry index (weight ÷ weight at 50th percentile/length ÷ length at 50th percentile).[13] A symmetry index >1.2 was used to define macrosomia in this study. Gestational age was assigned on the basis of menstrual dates confirmed by ultrasonography, or by ultrasonography in the absence of reliable menstrual dates. Birth weight and birth length percentile ranks were derived from Lubchenco.[14]

As can be seen in Table I, nine theoretic patterns of fetal growth were considered on the basis of AC percentile at the time of AC_1 (<24 weeks) and AC_2 (>32 weeks). Each of the 52 infants of diabetic mothers was assigned to an ultrasonographic growth pattern without knowledge of metabolic and anthropometric data. Three predominant patterns of growth were ascertained: group I (AC_1 ≤90th, AC_2 ≤90th), denoted normal growth; group II (AC_1 ≤90th, AC_2 >90th), denoted late accelerated growth; group III (AC_1 >90th, AC_2 >90th), denoted early accelerated growth. These three growth patterns included 47 of 52 infants of diabetic mothers. Analyses were on the basis of these 47 infants of diabetic mothers and the 19 control patients. Data were analyzed with the two-tailed Student t test, χ^2 or analysis of variance with posthoc Duncan comparison where appropriate.

Results

The maternal and neonatal anthropometric data for the three study groups and controls are presented in Table II. Those infants with normal abdominal circumference growth (group I, $n = 17$) were similar in weight and length to control infants. In contrast the infants of diabetic mothers in those groups with early (group III, $n = 13$) and late (group II, $n = 17$) accelerated AC growth had neonatal anthropometrics suggestive of diabetic macrosomia on the basis of birth weight and symmetry index of >1.2.

Examination of metabolic parameters (Table III) showed that all conventional measures of maternal metabolic control (i.e., fasting plasma glucose and hemoglobin A_{1c} levels) were significantly different in infants of diabetic mothers than in controls. However, infants of diabetic mothers from all groups had similar fasting plasma glucose and hemoglobin A_{1c} levels despite the described differences in neonatal anthropometrics. The mean number (± 1 SD) of fasting plasma glucose values in each patient used to generate average fasting plasma glucose were 23 ± 6.3 and 13.6 ± 2.5 in diabetic patients and controls, respectively. As expected, group II with late accelerated AC growth had measures of amniotic fluid insulin that tended to be higher than those in group I (normal growth).

Group III (early accelerated growth) was different in several respects. Amniotic fluid insulin and amniotic fluid insulin/glucose ratio was more similar to group I (normal growth) despite neonatal anthropometrics consistent with macrosomia. In addition, 6 of 13 infants in this group III had a biparietal diameter that exceeded the 90th percentile after 32 weeks' gestation (BPD_2 >90th). This finding occurred in only 1 of 34 infants of diabetic mothers in groups I and II ($p < 0.05$) and prompted stratification of group III on the basis of normal BPD growth (BPD_2 <90th, III-A) or accelerated BPD growth (BPD >90th III-B). Infants in group III with normal BPD growth (III-A) exhibited high hemoglobin A_{1c} levels in the first trimester and tended to have elevated amniotic fluid insulin and amniotic fluid insulin/glucose ratio in the third trimester (Table IV). By contrast, those with accelerated BPD growth (III-B) had significantly lower maximal and first-trimester hemoglobin A_{1c} and did not exhibit elevated amni-

Table II. Maternal and neonatal anthropometric data

	Group					
	Control	*I* $AC_1 \leq 90th$ $AC_2 \leq 90th$	*II* $AC_1 \leq 90th$ $AC_2 > 90th$	*III* $AC_1 > 90th$ $AC_2 > 90th$	*ANOVA*	*Group differences by Duncan ($p < 0.05$)*
Maternal						
Height (cm)	161 (8.2)	163 (7)	162 (8)	165 (8)	NS	
PIBW	111 (22.2)	110 (25)	114 (35)	97 (10)	NS	
Neonatal						
Birth length (cm)	50.5 (2.4)	50.1 (2.4)	51.1 (2.0)	52.5 (3.6)	NS	
Birth weight (gm)	3304 (534)	3309 (424)	3996 (648)	4095 (688)	<0.0001	C, I vs II, III
Symmetry index	1.02 (0.12)	1.08 (0.10)	1.29 (0.18)	1.28 (0.16)	<0.0001	C, I vs II, III
Symmetry index ≥ 1.2	2	3	11	9	<0.005*	C, I vs II, III

ANOVA, Analysis of variance; *PIBW,* prepregnant percent ideal body weight. Numbers in parentheses represent 1 SD.
*χ^2

Table III. Maternal and fetal metabolic data

	Group					
	Control	*I* $AC_1 \leq 90th$ $AC_2 \leq 90th$	*II* $AC_1 \leq 90th$ $AC_2 > 90th$	*III* $AC_1 > 90th$ $AC_2 > 90th$	*ANOVA*	*Group differences by Duncan ($p < 0.05$)*
Maternal fasting plasma glucose (mg/dl)						
Mean first trimester		122 (43)	121 (24)	114 (37)	NS	
Mean second trimester	73 (9)	117 (41)	116 (19)	125 (26)	<0.0001	C vs I, II, III
Mean third trimester	75 (8)	103 (24)	102 (15)	105 (26)	<0.0001	C vs I, II, III
Overall	74 (7)	110 (28)	108 (12)	111 (22)	<0.0001	C vs I, II, III
Maternal hemoglobin A_{1c}						
Maximum	5.3 (0.5)	7.5 (1.6)	7.4 (1.2)	7.9 (1.6)	<0.0001	C vs I, II, III
Mean first trimester		7.2 (2.0)	7.5 (1.2)	7.1 (1.7)	NS	
Mean second trimester	4.5 (0.7)	5.8 (1.3)	5.8 (1.1)	6.2 (1.0)	0.002	C vs I, II, III
Mean third trimester	4.4 (0.5)	5.9 (1.1)	5.4 (.90)	5.8 (0.9)	<0.0001	C vs I, II, III
Overall	4.4 (0.5)	6.2 (1.3)	6.1 (1.3)	6.0 (0.9)	0.0001	C vs I, II, III
Amniotic fluid insulin (μU/ml)	—	14.4 (10.6)	29.2 (28.6)	19.0 (22.2)	NS	
Amniotic fluid insulin/glucose (μU/ml)	—	45.8 (49.4)	111.8 (104.9)	48.4 (47.5)	0.05	II vs I, III

ANOVA, Analysis of variance. Numbers in parentheses represent 1 SD.

otic fluid insulin and amniotic fluid insulin/glucose ratio. Furthermore those infants with accelerated BPD growth were born to mothers who tended to be tall and lean.

Comment

Previous studies have shown that ultrasonography can detect evolving macrosomia in the fetus of a diabetic mother. In an earlier report from this center, Ogata et al.[4] described two patterns of fetal growth in pregnancy complicated by diabetes. One pattern was indistinguishable from that seen in nondiabetic pregnancies. The other pattern, designated as having accelerated growth on the basis of a disproportionate increase in abdominal circumference, resulted in heavier and fatter infants with evidence of augmented fetal islet function. Landon et al.[5] confirmed Ogata's findings, but neither study related growth to detailed measures of maternal metabolic control. We have now correlated fetal growth patterns to maternal metabolism. Our measures of maternal metabolic control were limited to fasting plasma glucose levels and hemoglobin A_{1c} because at the time this study was undertaken postprandial glucose measurements were not routinely performed. Fasting plasma glucose values obtained at predetermined regular intervals throughout gestation were used to generate average fasting plasma glucose values to characterize the maternal metabolic milieu. All values from weekly or biweekly outpatient visits were included. However, only two per week from inpatients were used so as not to bias the data with values obtained during relatively short periods of intense monitoring.

Our group has reported elevated levels of cord

Table IV. Infants of diabetic mothers with early accelerated growth separated by (BPD) growth

	Group		
	III-A $BPD_2 < 90th$ $n = 7$	*III-B* $BPD_2 > 90th$ $n = 6$	*p Value*
Maternal			
height (cm)	161 (8)	170 (7)	0.08
% Ideal body weight	102 (12)	93 (6)	NS
Neonatal			
Birth length (cm)	51.3 (4)	53.9 (2)	NS
Birth weight (gm)	3807 (544)	4430 (728)	NS
Symmetry index	1.2 (0.1)	1.4 (0.2)	NS
Maternal fasting plasma glucose (mg/dl)			
Mean first trimester	122 (43)	96 (12)	NS
Mean second trimester	126 (35)	124 (13)	NS
Mean third trimester	106 (31)	104 (20)	NS
Overall	113 (27)	109 (18)	NS
Maternal hemoglobin A_{1c}			
Maximum	9.3 (1.5)	6.9 (0.8)	0.009
Mean first trimester	8.3 (1.0)	5.4 (0.5)	0.008
Mean second trimester	6.4 (1.2)	6.0 (0.9)	NS
Mean third trimester	5.9 (1.0)	5.7 (0.9)	NS
Overall	6.6 (0.9)	5.7 (0.7)	NS
Amniotic fluid insulin (μU/ml)	28.0 (27.7)	8.5 (4.2)	NS
Amniotic fluid insulin/glucose (μU/ml)	70.5 (55.48)	22.6 (15.0)	0.06

Numbers in parentheses represent 1 SD.

plasma C-peptide and amniotic fluid insulin in association with higher birth weight in pregnancies complicated by mild gestational diabetes mellitus (GDM with fasting plasma glucose values <105 mg/dl) as well as in those with more severe GDM or pregestational insulin-dependent diabetes mellitus. This promoted the suggestion that fetal islet function may be exquisitely sensitive to alterations in maternal metabolism that are not appreciated by present methods of assessing metabolic control that focus exclusively on glucoregulation. The findings in the present report are consistent with that premise. The infants of diabetic mothers of group II (typical diabetic fetopathy) had the highest amniotic fluid insulin and insulin/glucose concentration, indicating fetal hyperinsulinism. However, their third-trimester glycemic control was good as evidenced by fasting plasma glucose values and hemoglobin A_{1c} not distinguishable from those of group I whose growth pattern was normal and amniotic fluid insulin level only mildly elevated.

The infants in our study who showed normal fetal AC growth (group I) and late accelerated AC growth (group II) conformed to those patterns first described by Ogata. Group I had birth anthropometrics indistinguishable from controls. Group II were heavier and fatter (symmetry index, 1.29) and showed evidence of fetal hyperinsulinism. The opportunity to analyze serial measurements starting earlier in pregnancy than in previous studies in a group restricted to pregestational diabetic patients provided an opportunity to identify a third pattern of growth not recognized heretofore. These fetuses showed acceleration of AC growth before 24 weeks' gestation, which was sustained at >90th percentile (Group III). The birth weight and symmetry index of these infants of diabetic mothers were similar to those of infants in whom accelerated AC growth was not detected until later in gestation. However, group III was also heterogeneous with respect to BPD growth. Those with normal BPD growth tended to have evidence of fetal hyperinsulinism and neonatal anthropometrics typical of diabetic fetopathy. Furthermore, the hemoglobin A_{1c} values suggest that these women may have been in poorer control early in pregnancy. It should be noted that this was the only subset in which conventional measurements of maternal metabolic control may have indicated that the group was at risk of macrosomia.

Six of 13 group III patients with early accelerated AC growth (group III-B) also had accelerated growth of the biparietal diameter. These infants of diabetic mothers were also disproportionately heavy (symmetry index, 1.4). Whether this truly represents adiposity typical of diabetic fetopathy cannot be determined. There was no evidence of poor metabolic control in the first trimester as in group III-A and amniotic fluid insulin measurements were similar to concentrations we have found in normal nondiabetic pregnancies.[11] Furthermore, the mothers of these infants tended to be the tallest and leanest of any subset, an indication that these infants may have been destined to be large on the basis of genetic or other factors.

In summary, most of our infants of diabetic mothers

experienced longitudinal growth patterns consistent with those previously described. However, we also identified a group of infants of diabetic mothers that exhibited excessive abdominal circumference growth earlier than predicted (i.e., before 24 weeks' gestation). Within this group, those with normal biparietal diameter growth showed heightened islet cell function similar to that previously described in diabetic fetopathy and found in our group II with classic diabetic macrosomia. Those with accelerated biparietal diameter growth had increased birth weight and high symmetry index as expected but without evidence of fetal hyperinsulinism. Whether this pattern represents a previously unrecognized or variable response to early derangements in maternal metabolism or an expression of genetically determined accelerated growth potential remains to be established.

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Prevalence and etiology of respiratory distress in infants of diabetic mothers: Predictive value of fetal lung maturation tests

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The purpose of this study was to investigate the prevalence of respiratory distress syndrome attributable to surfactant deficiency in infants of diabetic mothers tested for fetal lung maturation. Three tests were assessed: (1) lecithin/sphingomyelin ratio, (2) phosphatidylglycerol concentration, and (3) optical density at 650 nm. From January 1987 through June 1989, 526 diabetic gestations were delivered within 5 days of fetal lung maturation testing. Surfactant-deficient respiratory distress syndrome was present in five infants (0.95%); all were <34 weeks' gestational age. Other causes of respiratory distress were transient tachypnea of the newborn (n = 5), hypertrophic cardiomyopathy (n = 4), pneumonia (n = 2), polycythemia (n = 1), and meconium aspiration syndrome (n = 1). The use of standard maturity values of lecithin/sphingomyelin ratio ≥ 2.0, phosphatidylglycerol > 2% to 5%, and optical density at 650 nm ≥ 0.150 were evaluated. Each test had a 100% sensitivity in identifying surfactant-deficient respiratory distress syndrome and a 100% negative predictive value in identifying the absence of disease. All three tests had a low positive predictive value: 15% for lecithin/sphingomyelin ratio, 9% for phosphatidylglycerol, and 3% for optical density at 650 nm. We concluded that most cases of respiratory distress in the infants of diabetic mothers were unrelated to surfactant deficiency. The standard maturity values used in fetal lung maturation tests were valid in the diabetic gestation. The optical density at 650 nm was useful as a first-line test to predict the absence of surfactant-deficient respiratory distress syndrome. (Am J Obstet Gynecol 1990;163:898-903.)

Key words: Respiratory distress syndrome, diabetes in pregnancy, fetal lung maturation, surfactant deficiency

Respiratory distress syndrome (RDS) describes a constellation of clinical findings in which the cardinal signs are tachypnea, expiratory grunting, nasal flaring, and costal retractions. Its cause is deficient surfactant production (as established by amniotic fluid analysis) producing decreased lung compliance with resultant hypoxia.[1] Surfactant-deficient RDS has been reported to occur more frequently in infants of diabetic mothers. The ability to determine the lecithin/sphingomyelin (L/S) ratio has offered the clinician a means to prevent iatrogenic prematurity while avoiding intrauterine death in diabetic pregnancies. Several earlier studies have supported a delayed biochemical maturation of the fetal lung in the "uncomplicated" diabetic gestation.[2-6] Phosphatidylglycerol heralds the final step in fetal lung maturation.[7] It has been suggested that the presence of phosphatidylglycerol assures the absence of surfactant-deficient RDS in infants of diabetic mothers.[3-7] More recently, however, the evidence of delayed fetal lung maturation in diabetic gestations has not been substantiated.[8-11] Two reports failed to demonstrate differences in fetal lung maturation among diabetic gestations relative to classification.[8,9] In addition, delays in maturation of the L/S ratio or in the appearance of phosphatidylglycerol could not be demonstrated in diabetic gestations when compared with normal gestations.[9-11]

Other obstetric advances have facilitated safer expectant management and thus have contributed to a reduced prevalence of RDS in infants of diabetic mothers. These include improved methods of glycemic control, more accurate dating of gestational age by ultrasonography, antepartum fetal surveillance, and improved neonatal care. These factors were examined by Mimouni et al.,[12] who concluded that diabetes, as currently managed, did not increase the risk for development of surfactant-deficient RDS.

The purpose of this study was to investigate the oc-

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currence of respiratory distress attributable to surfactant deficiency in infants of diabetic mothers relative to three methods of fetal lung maturation testing.

Material and methods

Study population. During the study period (January 1987 through June 1989), 1830 women whose pregnancies were complicated by diabetes were delivered at Women's Hospital, 584 of whom (32%) underwent amniotic fluid evaluation of fetal lung maturation. Of these, 526 were delivered of their infants within 5 days and were included in final analysis. Ninety-five percent of the study patients had a Spanish surname. Fetal lung maturation testing was undertaken more frequently in women with insulin-requiring diabetes: 17% of those with class A_1 were tested, compared with 47% of those with class A_2, 51% of those with class B, and 53% of those with class C through R during this period. The composition of the study population consisted of 22% class A_1 ($n = 114$), 68% class A_2 ($n = 358$), 6% class B ($n = 31$), and 4% class C through R ($n = 23$). Premature delivery before 37 completed weeks occurred in 82 patients (16%), 12 (2%) of whom were delivered before 34 completed weeks.

Pregnancy management. Patients with class A_1 gestational diabetes mellitus were managed with measurement of weekly fasting serum glucose levels, with values maintained at <105 mg/dl by diabetic diet therapy. Patients with class A_2 gestational diabetes mellitus (fasting serum glucose level ≥ 105 mg/dl) were evaluated by home capillary blood glucose monitoring four to six times a day; they maintained euglycemic blood glucose control by a combination of diet and insulin therapy. Patients with class B through R were followed up similarly to class A_2 patients but insulin regimens and monitoring of vascular complications were individualized as needed.

Indications for delivery and fetal lung maturation evaluation in term gestations (after 37 completed weeks, $n = 444$) were elective delivery (96%) and poor maternal glycemic control (4%). Indications in preterm gestations ($n = 82$) were labor (53%), rupture of membranes (23%), pregnancy-induced hypertension (8%), abnormal antepartum testing results (6%), and poor maternal glycemic control (4%). Amniotic fluid specimens from six patients with premature rupture of membranes were obtained from perineal pad extraction, as described by Golde.[13] The determination of optical density at 650 nm (OD_{650}) was not performed on these perineal pad specimens or on those contaminated by blood ($n = 8$) or meconium ($n = 26$). Clinically the value of OD_{650} was used as a rapid screening test when test results were necessary for immediate obstetric management. An OD_{650} value ≥0.150 was considered mature.[14] This was performed first by the house staff in 28 patients on the labor floor and later confirmed by the laboratory. No cases of false mature tests occurred, nor was there a significant difference between house staff and laboratory results. The laboratory value was used for analysis in this study. In nonemergent cases, the results of the L/S ratio and phosphatidylglycerol were used. Mature values were considered to be L/S ratio ≥ 2.0 and phosphatidylglycerol ≥ 2% to 5%.[7]

Outcome of neonates. The hospital courses of all infants were reviewed for confirmation of diagnosis with a staff neonatologist (F. J. W.) who was blinded to the fetal lung maturation test results. Those infants exhibiting signs of respiratory distress (tachypnea, expiratory grunting, nasal flaring, costal retractions, or cyanosis) are described in this study. Surfactant-deficient RDS was diagnosed with these criteria: (1) onset of clinical symptoms within 6 hours of life, with supplemental oxygenation required at >24 hours of life and peak severity at 2 to 3 days of life, and (2) chest x-ray film with diffuse reticulogranular pattern in both lung fields with superimposed air bronchograms.[1] Other causes of respiratory distress distinguished from surfactant-deficient RDS were transient tachypnea of the newborn, hypertrophic cardiomyopathy, pneumonia, meconium aspiration, and polycythemia (venous hematocrit ≥ 65%). Gestational age at delivery was determined by the clinical parameters of menstrual age, clinical age at first visit, and first ultrasonographic examination and subsequent growth pattern. In all cases there was correlation with neonatal estimation by Dubowitz score of gestational age within 2 weeks.

Performance of fetal lung maturation tests. All tests were performed in a certified pathology laboratory by a medical technologist. The lung profile was obtained with the two-dimensional thin-layer chromatography technique with acetone precipitation of disaturated lecithin (dipalmitoyl phosphatidylcholine) as described by Kulovich et al.[7] The OD_{650} was measured on uncontaminated, centrifuged (2000 *g* for 10 minutes) amniotic fluid with a Bausch-Lomb spectrophotometer (No. 20, at 340 to 800 nm) as described by Sbarra et al.[14]

Statistical analysis. Comparisons between mean values of continuous variables (e.g., OD_{650}, percent phosphatidylglycerol, L/S ratio, gestional age at delivery) and diabetic class were analyzed by analysis of variance. The correlation of immature test values and the presence or absence of surfactant-deficient RDS was assessed by Fisher's exact test. Sensitivity (percent of immature tests in infants with surfactant-deficient RDS), specificity (percent of mature tests in infants without surfactant-deficient RDS), positive predictive value (percent of surfactant-deficient RDS in infants with immature tests), and negative predictive values (percent without surfactant-deficient RDS in infants with mature

tests) were determined.[15] The test efficiency (True positive plus True negative/Total) also was calculated.

Results

One complication (1/526) from amniocentesis, a transplacental "bloody tap," occurred. Persistent fetal bradycardia and bleeding from the placental site was visualized on ultrasonography, necessitating emergency cesarean section. This neonate had a hematocrit of 29% and exhibited hypovolemic shock with metabolic acidosis, necessitating dopamine administration and blood transfusion. The infant responded well and was discharged home on the third day of life.

Eighteen neonates had signs of respiratory distress consisting of tachypnea, grunting, costal retractions, or cyanosis, occurring within the first 6 hours of life and requiring further workup. Causes of these symptoms are presented in Table I and discussed below.

Surfactant-deficiency RDS (cases 1 to 5). Surfactant-deficient RDS was present in five (0.95%) infants. Three of them had severe surfactant-deficient RDS with one dying on the first day of life and the other two requiring oxygen therapy for 26 and 31 days. The remaining two had mild surfactant-deficient RDS, both requiring oxygen for the first 48 hours. One of these infants also had apnea-bradycardia spells that necessitated aminophylline therapy during the first month of life.

Transient tachypnea of the newborn (cases 6 to 10). Five infants were diagnosed with transient tachypnea of the newborn. All were born via cesarean section, four before labor and the fifth during early labor with intervention for fetal distress. They were rapidly weaned off supplemental hood oxygen within the first 6 hours of life. Chest x-ray films showed areas of atelectasis in four of the five cases.

Hypertrophic cardiomyopathy (cases 11 to 14). Four of the infants with respiratory distress were diagnosed by echocardiogram to have hypertrophic cardiomyopathy (with intraventricular septal hypertrophy). Chest x-ray films showed pulmonary edema in two cases and cardiac enlargement in the third. No infant had signs of sepsis, shock, or asphyxia. Two of these infants required oxygen therapy after the first day of life. One infant (case 14) had respiratory distress and a diffuse granular pattern on chest x-ray film. The clinical course, coupled with an echocardiographic persistence of hypertrophic cardiomyopathy at 16 days of life and the failure of an increase in positive inspiratory pressure to improve oxygenation, implicated a cardiogenic origin of the respiratory distress. All of the four mothers of these infants initially were seen for prenatal care with overt fasting hyperglycemia (137 to 228 mg/dl). Two of these mothers (cases 11 and 12) had late entry into prenatal care and late diagnosis of diabetes; they were begun on insulin at 30 and 25 weeks, respectively. Patients 13 and 14 both presented for care and had the diagnosis made in the first trimester. However, both were extremely noncompliant with prenatal care, diet, and insulin therapy.

Pneumonia (cases 15 and 16). Two infants were diagnosed with pneumonia. One had β-hemolytic streptococcal bacteremia and required oxygen therapy by hood for 2 days. The second was born to a mother admitted with premature rupture of the membranes and amnionitis. She received intrapartum antibiotic therapy. The infant's chest x-ray film showed a bilateral diffuse granular pattern with a right upper lobe infiltrate. The infant's clinical course was consistent with pneumonia necessitating oxygen therapy by hood for 7 days.

Of the remaining two symptomatic infants (cases 17 and 18), one was first seen with tachypnea requiring oxygen by hood for the first 6 hours of life. This infant had polycythemia (hematocrit 66%) and required a partial exchange transfusion. The other had severe meconium aspiration syndrome with acidosis, shock, and persistent fetal circulation.

Correlation of tests with surfactant-deficient RDS. All 526 specimens had an L/S ratio and phosphatidylglycerol determined. Forty-four (8.3%) of the samples, including three of the five infants with surfactant-deficient RDS, were contaminated. None of these infants with contaminated specimens who had an L/S ratio ≥2.0 or phosphatidylglycerol ≥5% exhibited surfactant-deficient RDS ($p < 0.01$). There was a significant correlation between all three tests and the development of surfactant-deficient RDS (Fisher's exact test, $p < 0.02$, Table II). All three tests had a 100% sensitivity (all infants with surfactant-deficient RDS were identified by immature test values) and had 100% negative predictive values (no infants with mature test values had surfactant-deficient RDS). The specificity of all tests was relatively high, probably reflecting the fact that 85% of the infants were born at term (i.e., after 37 completed weeks). Surfactant-deficient RDS was not present in any term infants. In the limited number of infants with fetal lung maturation evaluations who were delivered before 34 weeks' gestation, 42% (5/12) exhibited surfactant-deficient RDS.

The L/S ratio had the best positive predictive value, but it was still very poor (15%). The lowest positive predictive value (3.2%) was seen with the OD_{650}. With a mature OD_{650} value ≥ 0.150, only 5 of 419 (1.2%) had an L/S ratio < 2.0 ($p < 0.001$). The presence of phosphatidylglycerol did not improve the predictive ability of the L/S ratio. In all cases where phosphatidylglycerol was present, the L/S ratio was >2.0. Overall, the L/S ratio had the greatest test efficiency of 94.7%, compared with phosphatidylglycerol (90.5%) and OD_{650} (86.9%).

Table I. Clinical characteristics of infants of diabetic mothers with respiratory distress (tachypnea, grunting, or costal retractions)

Patient No.	*Gestational age (wk)*	*Weight (gm)*	*Sex*	*L/S ratio*	*PG (%)*	*OD 650**	*Obstetric complication†*	*Diagnosis*
1	28	820	M	1.0	0	Bloody	Severe PIH; IUGR; CS; class A_2	Severe surfactant-deficient RDS, 26 days oxygen therapy
2	24	700	F	1.1	0	Perineal pad	PROM, PTL; vaginal birth; class B	Severe surfactant-deficient RDS (β-hemolytic streptococci), Neonatal death
3	31	1500	M	0.8	0	0.060	PTL; repeat CS; class A_2	Severe surfactant-deficient RDS, 31 Days oxygen therapy Untreated diabetes
4	32	2190	F	1.7	0	Perineal pad	PROM, PTL; CS; breech; class A_2	Mild surfactant-deficient RDS, 2 Days oxygen therapy
5	33	2605	M	1.6	0	0.050	PROM, PTL; vaginal birth; class A_2	Mild surfactant-deficient RDS, 2 Days oxygen therapy, Apneic spells
6	37	2880	M	2.4	0	0.340	Repeat CS; class A_1	TTN, Atelectasis on chest x-ray film
7	39	4700	M	3.2	25	0.900	Repeat CS; class A_2	TTN, Atelectasis on chest x-ray film
8	37	2960	M	3.1	5	0.105	Repeat CS; class A_1	TTN, Atelectasis on chest x-ray film
9	34	2400	M	2.6	18	0.350	PTL, CS; class RF	TTN, Clear chest x-ray film
10	31	2200	F	2.4	0	0.130	PTL, CS; class A_1	TTN, Atelectasis on chest x-ray film
11	37	4900	M	4.9	24	1.000	Repeat CS; class A_2	Mod. HCM and PDA on ECHO, Pulmonary edema on chest x-ray film
12	37	4600	M	2.7	0	0.450	Repeat CS; class A_2	Mild HCM on ECHO, Pericardial effusion, 2 days oxygen hood therapy
13	36	4080	F	3.3	25	0.360	Repeat CS; class A_2	Mod. HCM on ECHO, Pulmonary edema on chest x-ray film
14	36	3920	M	1.7	0	0.190	Repeat CS; class A_2	Mod. HCM and PDA on ECHO, Outflow obstruction, Intubated 6 days
15	39	4140	M	3.1	18	0.400	Repeat CS; class C	Pneumonia (β-hemolytic streptococci), 3 days oxygen hood therapy
16	37	3060	F	1.5	0	0.090	Repeat CS; class A_2	RUL pneumonia, 7 days oxygen hood therapy
17	42	3720	M	1.1	0	Meconium	Repeat CS; class A_1	Severe meconium aspiration, Shock
18	34	2580	M	1.8	0	0.080	PTL; vaginal birth; class A_2	Polycythemia, Partial exchange transfusion

PG, Phosphatidylglycerol; *PIH*, pregnancy-induced hypertension; *IUGR*, intrauterine growth reatardation; *CS*, cesarean section; surfactant deficient RDS; *PROM*, premature rupture of the membranes; *PTL*, preterm labor; *TTN*, transient tachypnea of the newborn; *HCM*, hypertrophic cardiomyopathy; *ECHO*, echocardiogram; *PDA*, patent ductus arteriosus; *RUL*, right upper lobe.

*Reason for not performing OD $_{650}$ given, i.e., perineal pad collection, bloody or meconium-stained fluid.

†American College of Obstetricians and Gynecologists modification of White diabetic classification (A_1, A_2, B, or C) is listed.

RDS did not develop in any of the 58 infants not delivered within 5 days of fetal lung maturation. Sixty-four percent had a mature L/S ratio, with 85% delivered within 14 days of amniocentesis. The mean number of days to delivery was 12 and the mean gestational age at amniocentesis was 37 weeks. The delay in delivery was primarily due to lack of labor room space for elective induction. Of the 36% with an immature L/S ratio, 51% were delivered within 14 days of amniocentesis with the mean number of days to delivery being 18 and the mean gestational age at amniocentesis being 36 weeks.

Table II. Comparison of predictive ability of three tests for fetal lung maturation. Actual numbers of patients are presented as ratios in parentheses below calculated value of predictive test

Test	*Sens.*	*Spec.*	*PPV*	*NPV*	*Efficiency*	*p**
L/S ratio < 2.0	100%	94.6%	15.0%	100%	94.7%	<0.001
	5/5	493/521	5/33	493/493	498/526	
Phosphatidylglycerol	100%	90.4%	9.0%	100%	90.5%	<0.001
< 2%	5/5	471/521	5/55	471/471	476/526	
OD_{650} < 0.150	100%	87.0	3.2%	100%	86.9%	.0017
	2/2	419/480	2/61	419/419	421/482	

Sens., Sensitivity; *Spec.*, specificity; *PPV*, positive predictive value; *NPV*, negative predictive value.
*Fisher's exact p value for the association of each test with the development of surfacant deficient RDS.

There was no significant difference in mean gestational age (±SEM) at time of delivery between the various diabetic classes: class A_1, 38.0 ± 0.2 weeks; class A_2, 38.0 ± 0.1 weeks; class B, 37.0 ± 0.5 weeks; classes C through R, 37 ± 0.3 weeks. Likewise, the mean value for all three tests (L/S ratio, percent phosphatidylglycerol, and OD_{650}) did not differ significantly among the diabetic classes ($p > 0.10$).

Comment

Of the 18 infants evaluated for signs of respiratory distress, only five were found to have surfactant-deficient RDS (<1%); all five were delivered before 34 weeks' gestational age. Other causes were responsible for respiratory distress in the remaining 13 infants. The five infants with transient tachypnea of the newborn were delivered via cesarean section. A complicating finding was that four of the infants with symptoms were found to have hypertrophic cardiomyopathy with intraventricular septal hypertrophy. Without a high degree of suspicion by the clinican and echocardiography, this complication of diabetes could easily be attributed to surfactant-deficient RDS. All four were subject to poor maternal glycemic control, either from late diagnosis with marked fasting hyperglycemia or from poor therapeutic compliance. This association between septal hypertrophy is well correlated with poor maternal diabetic control and fetal hyperinsulinemia.[16-20] Last, pneumonia was also found to be a cause of significant respiratory distress in two of the infants, both of whom required oxygen.

This study confirms the use of standard maturity values of L/S ratio ≥ 2.0, phosphatidylglycerol > 2% to 5%, and OD_{650} ≥ 0.150 as valid in the diabetic pregnancy. All infants with surfactant-deficient RDS were identified by immature values with each of the three tests (sensitivity = 100%), while surfactant-deficient RDS was not seen in any infants with mature tests. This study extends the application of the OD_{650} to the diabetic pregnancy as an ideal primary test.[21-25] It is rapid, and inexpensive, and it maintains a high negative predictive value.

In summary, in this large clinical series managed by current obstetric standards, surfactant-deficient RDS was rare in the infants of diabetic mothers. The majority of infants exhibiting signs of respiratory distress did not have immature lung development with insufficient surfactant production. Furthermore, surfactant-deficient RDS was not present in any term infants. We suggest it is time to reevaluate the need for fetal lung maturation testing in term, currently managed diabetic pregnancies.

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The relationship between maternal serum and amniotic fluid α-fetoprotein in women undergoing early amniocentesis

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α-Fetoprotein levels were measured on 148 paired samples from the maternal serum and amniotic fluid in women ≥age 35, who were undergoing early amniocentesis (12 to 14 weeks) for chromosomal analysis. These 148 women were white, weighed <200 pounds, had no serious medical problems, and did not have a fetal abnormality detected by ultrasonography or karyotype analysis. There was a significant rise in the maternal serum α-fetoprotein concentration from 12 to 14 weeks' gestation. Amniotic fluid α-fetoprotein peaked at 13 weeks and then significantly declined by 14 weeks' gestation. Similar to reports from normal pregnancies at 16 and 17 weeks, we found no correlation between the maternal serum and amniotic fluid α-fetoprotein levels between 12 and 14 weeks. Amniotic fluid α-fetoprotein levels cannot be predicted by levels in the maternal serum in pregnancies between 12 and 14 weeks' gestation. (AM J OBSTET GYNECOL 1990;163:903-6.)

Key words: Maternal serum, amniotic fluid, α-fetoprotein

Recently new techniques such as chorionic villus sampling[1] and early amniocentesis[2] have been developed that allow genetic disorders to be diagnosed in the first trimester. It has been predicted that the use of these procedures will make first-trimester prenatal diagnosis the norm for the 1990s.[3] A possible advantage of early amniocentesis over that of chorionic villus sampling is the use of amniotic fluid α-fetoprotein (AFP) analysis to detect a fetal neural tube defect. Amniotic fluid AFP medians have been reported in gestations from 11 to 15 weeks in over 1000 pregnancies.[4] However, the reliability of maternal serum or amniotic fluid AFP to accurately diagnose open spine disorders in these early pregnancies is still under investigation.[5, 6] Whereas Barford et al.[7] found no correlation between maternal serum and amniotic fluid AFP at 16 and 17 weeks' gestation, this relationship has not been ascertained in earlier gestations of 11 to 14 weeks.

To assess the correlation between AFP levels in the

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Table I. Mean AFP levels in maternal serum and amniotic fluid with standard errors

Gestation (wk)	n	Maternal serum AFP (ng/ml)		Amniotic fluid AFP (μg/ml)	
		Mean	SEM	Mean	SEM
12	25	15.96	1.25	18.20	0.94
13	38	20.96	1.13	21.58	0.72
14	85	28.63	1.62	18.14	0.58

maternal serum and amniotic fluid compartments, we reviewed the records of women who underwent an early amniocentesis (11 to 14 weeks) at our institution during a 1-year period. The relationship between AFP in the maternal serum and amniotic fluid in these pregnancies form the basis of our report.

Material and methods

An early amniocentesis, in our study population, was defined to be from 11 through 14 completed weeks of gestation when the amniocentesis was performed. Before each amniocentesis a maternal serum sample was obtained for an α-fetoprotein assay. An ultrasonographic examination was then performed to document fetal viability and to confirm gestational age. If the best estimate of gestational age by ultrasonography agreed within 7 days of a reliable last menstrual period, then the menstrual dates were used to date the pregnancy. If the menstrual dates were uncertain or if the best estimate of gestational age by ultrasonography varied by more than 7 days from the last menstrual period, then the ultrasonographic best estimate of gestational age was used to date the pregnancy.

Amniocentesis was performed by standard technique with a 22-gauge needle and ultrasonographic guidance. A total of 15 ml of amniotic fluid was withdrawn for a fetal karyotype analysis and an amniotic fluid AFP assay. The AFP samples from the maternal serum and amniotic fluid on each patient were measured in the same reference laboratory with an enzyme immunoassay technique (Abbott polyclonal). The intraassay and interassay coefficients of variation on the AFP samples reported in our study were 6.4% and 7.1%, respectively.

From Aug. 1, 1988, through July 31, 1989, after Institutional Review Board approval, women were prospectively identified and informed consent was obtained for an early genetic amniocentesis. Patients were included if they were white, weighed <200 pounds, had no serious medical problems, and had a singleton gestation between 11 and 14⅞ weeks' gestation. Patients were excluded from analysis if a fetal ultrasonogram or chromosomal abnormality was identifed or if they were at increased risk of having an infant with a neural tube defect.

Analysis of variance with Duncan's multiple range test was used to compare serum and amniotic fluid AFP levels at each week of gestation. Pearson's correlation coefficient was used to define the relationship beween maternal serum and amniotic fluid AFP levels.

Results

One hundred forty-eight paired maternal serum and amniotic fluid AFP samples were obtained at 12, 13, and 14 weeks' gestation. Patients seen at 11 weeks' gestation were excluded because of insufficient numbers. These 148 women all had an early amniocentesis for advanced maternal age. The mean maternal age was 37 years. All infants born to these women were normal at birth with no evidence of a neural tube defect.

Mean AFP levels in the serum and amniotic fluid with standard errors at each week of gestation are listed in Table I. Maternal serum AFP values were significantly higher at week 14 than at weeks 12 and 13 ($p = 0.0001$; by analysis of variance). Amniotic AFP values were significantly higher at week 13 than at weeks 12 and 14 ($p = 0.002$; by analysis of variance). Fig. 1 depicts the relationship between maternal serum AFP and amniotic fluid AFP in gestations from 12 to 14 weeks. No correlation between AFP levels in the serum and amniotic fluid compartment was noted ($r = -0.071$).

Comment

It has been shown by the study of human fetuses[8] that serum levels of AFP rapidly increase each week of gestation beginning at 6 weeks and reaching a maximal concentration at 13 weeks. The rapid increase in AFP concentration during this time in gestation is thought to correlate with the rapid growth of the fetal liver, the primary source of AFP production.[9]

Crandall et al.[4] reported that the amniotic fluid AFP levels parallel the levels in fetal serum from 11 to 15 weeks' gestation, although at approximately 120 times lower in concentration. These levels peak at 13 weeks and then decline by 10% each week thereafter. AFP levels in our 148 amniotic fluid samples from 12 to 14 weeks' gestation confirmed this relationship.

Hay et al.[10] reported that maternal serum AFP in normal human pregnancies could be detected by radioimmunoassay as early as 10 weeks' gestation and gradually rose each week in gestation until a peak level was obtained at 32 weeks. Our data and those of others[11, 12] confirm that maternal serum AFP levels rise each week of gestation beginning in the first trimester.

Barford et al.[7] found no relationship between maternal serum and amniotic fluid AFP in 297 paired serum and amniotic fluid samples from normal pregnancies at 16 to 17 completed weeks of gestation. To date, this relationship between the serum and amniotic fluid AFP compartments has not been assessed in ear-

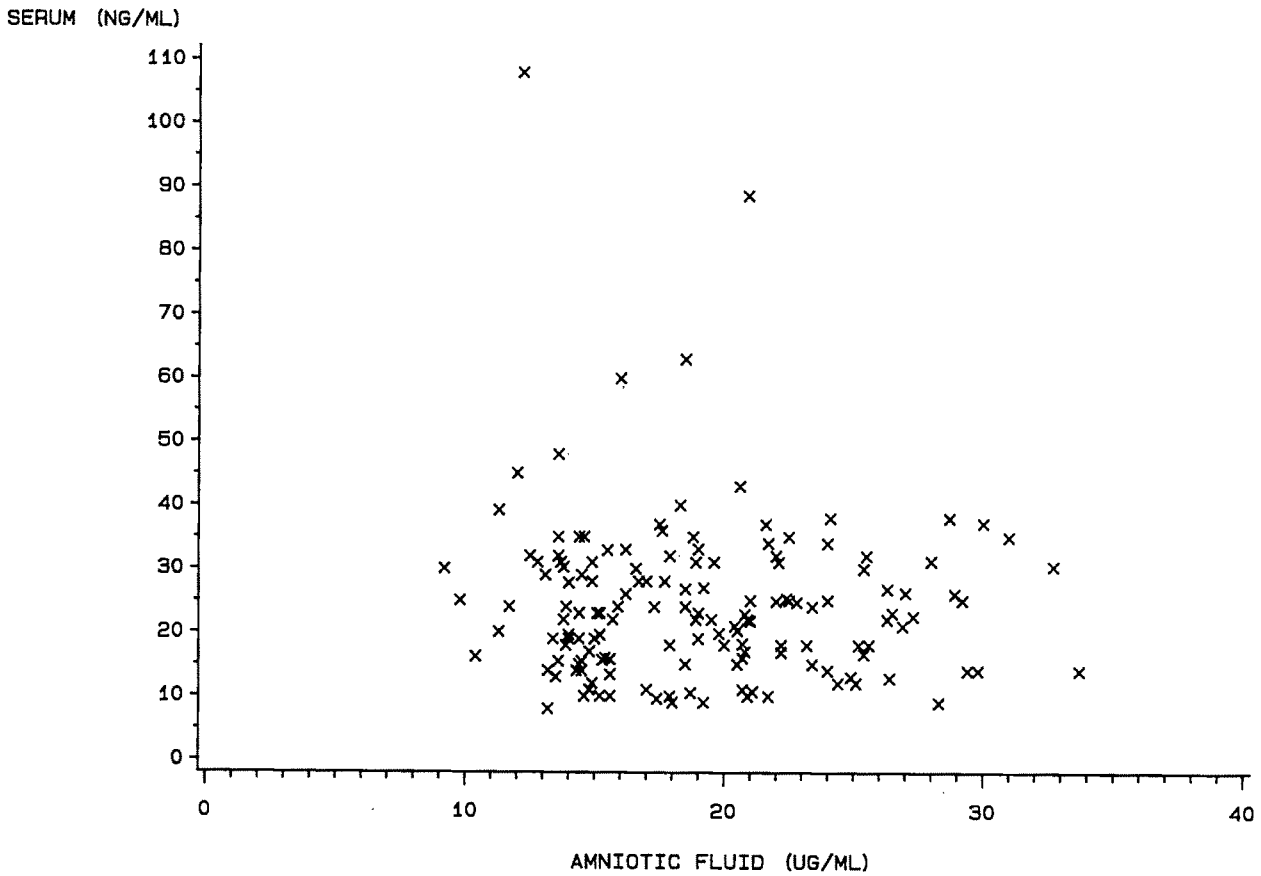


Fig. 1. Relationship between maternal serum AFP and amniotic fluid AFP in gestations between 12 and 14 weeks.

lier gestations. In this study we could not find a statistical relationship between maternal serum and amniotic fluid AFP levels in 148 paired samples obtained from 12- to 14-week gestations.

Mears et al.[13] used iodine 125–labeled AFP during the last trimester of pregnancy in the pregnant ewe to demonstrate rapid transplacental transfer of AFP between the fetal and maternal serum. However, there was much slower transfer between the amniotic fluid and fetal and maternal serum. It was therefore concluded that the transfer of AFP between the fetus and mother is transplacental rather than transamniotic during the last third of pregnancy and that amniotic fluid AFP is a static pool when compared with AFP in fetal and maternal blood. In humans it has not been clearly defined how α-fetoprotein passes from the fetal compartment into the maternal serum. The absence of a relationship between AFP levels in the maternal serum and amniotic fluid compartments, as described by Barford et al.[17] at 16 and 17 weeks and by our study at 12 to 14 weeks' gestation, suggests, even as early as 12 weeks' gestation, that the placenta, the amnion, or both regulate this protein interchange.

The lack of a correlation between maternal serum and amniotic fluid in gestations from 12 to 14 weeks precludes the use of maternal serum AFP levels to predict amniotic AFP levels in women undergoing an early amniocentesis or perhaps a chorionic villus sampling. Although the predictive value for a fetus with a neural tube defect of either maternal serum or amniotic fluid AFP is not known for gestations before 14 weeks, fetal chromosomal aneuploidies have been found in association with low maternal serum AFP levels in pregnancies from 8 to 11 weeks' gestation.[12, 14] Sufficient studies relating elevated levels of maternal serum AFP with neural tube defects in the first trimester are not available, and large population studies will be required to determine the sensitivity and specificity of maternal serum AFP testing to detect open spine defects or other fetal anomalies in these early gestations. The reliability of amniotic fluid AFP determinations in early pregnancies to diagnose neural tube defects will be determined in part by the accuracy of acetylcholinesterase analysis to aid in the diagnosis of these disorders.[5, 6]

In summary, we could not find a correlation between AFP levels in the maternal serum and amniotic fluid in women undergoing genetic amniocentesis at 12 to 14 weeks' gestation. AFP levels in the maternal serum in

these early gestations cannot be used to predict AFP levels in the amniotic fluid.

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Perinatal outcome of forty-nine pregnancies complicated by acardiac twinning

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Acardiac twinning affects 1 in 100 monozygotic twin pregnancies and 1 in 35,000 pregnancies overall. The presence of an acadiac twin requires the normal (or "pump") twin to provide circulation for itself, as well as the acardiac sibling. In many cases the acardiac twin is almost equal in size to the normal twin. The principal perinatal problems associated with acardiac twinning are pump-twin congestive heart failure, maternal hydramnios, and preterm delivery. We reviewed the perinatal courses of 49 acardiac twin pregnancies to identify factors prognostic of favorable outcome. The overall perinatal mortality was 55%, primarily associated with prematurity. Mean (±SD) gestational age at delivery was 29 ± 7.3 weeks, with a mean (±SD) normal twin weight of 1378 ± 1047 gm. The acardiac weight averaged 651 ± 571 gm. However, the occurrence of hydramnios, the occurrence of preterm labor, and perinatal outcome were strongly related to the ratio of the acardiac and pump-twin's weight. The mean overall ratio of the twin weights was 52% ± 42%. However, the mean weight ratio for patients delivered before 34 weeks was 60% versus 29% ($p < 0.04$). Preterm delivery was strongly associated with the development of hydramnios and congestive heart failure in the pump twin ($p < 0.01$). If the twin-weight ratio was above 70% (25% of cases), the incidence of preterm delivery was 90%; hydramnios, 40%; and pump-twin congestive heart failure, 30% compared with 75%, 30%, and 10%, respectively, when the ratio was less ($p < 0.05$). Regression of the weight of the acardiac twin against its longest dimension (L) resulted in this equation for prediction of acardiac weight: Weight (grams) = $1.2\ L^2 - 1.7L$; $r = 0.79$, $p < 0.01$. These data suggest that estimation of the relative weights in acardiac twins provides prognostic information regarding outcome. Poor outcome occurs with congestive heart failure and hydramnios in the normal twin. Use of the above data may assist in counseling patients and determining optimal management. (Am J Obstet Gynecol 1990;163:907-12.)

Key words: Acardiac, twins, hydramnios

Acardiac twinning is a rare complication of multifetal gestation occurring in 1% of monozygotic twin pregnancies and 1 of 35,000 pregnancies overall.[1, 2] The presence of an acardiac twin requires the normal (or "pump") twin to provide circulation for itself as well as the acardiac sibling. In many cases the acardiac twin is equal in size to or larger than the normal co-twin. The principal perinatal problems associated with acardiac twinning are pump-twin congestive heart failure, maternal hydramnios, and preterm delivery.[3] Frequently these events occur in the periviable period (22 to 26 weeks). We therefore reviewed the obstetric histories and neonatal courses of 49 cases of acardiac twinning to identify factors prognostic of favorable outcome.

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6/6/22353

Methods

Cases were collected from records of in-born pregnancies at the University of California San Diego and from the case files of one of the authors (K. B.). For each case the maternal delivery record, pump-twin neonatal record and pertinent autopsy and pathologic reports were obtained.

Gestational age at delivery was determined by best obstetric dates supplemented with the Dubowitz score. The diagnosis of hydramnios was based on the clinical impression of the attending obstetrician together with sonographic reports. The diagnosis of pump-twin congestive heart failure was based on clinical observations by the attending neonatologist, and/or radiographic-sonographic evidence of cardiomegaly with coexisting ascites or edema and/or autopsy findings.

Twin-weight ratio was computed as the weight of the acardiac twin expressed as a percentage of the pump-twin weight. A total of 33/49 (66%) pregnancies contained adequate data for this analysis.

The data were collected in a microcomputer database

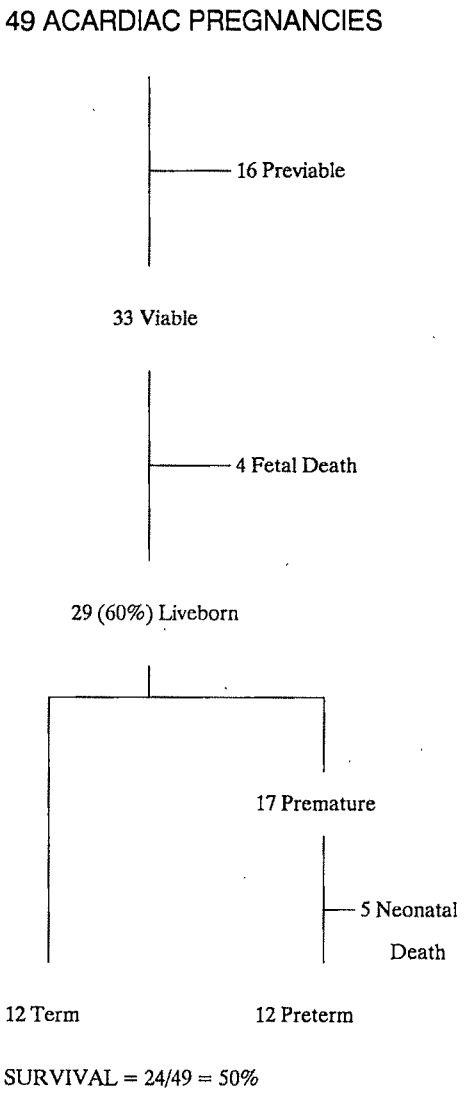


Fig. 1. Schematic of pregnancy outcome for 49 cases of acardia. Viability is defined as delivery at or beyond 25 weeks.

Table I. Perinatal complications of 49 pregnancies with acardiac twinning

Delivery mode	
Spontaneous abortion	18%
Elective termination	14%
Cesarean section, all cases	38%
Cesarean section, potentially viable cases	58%
Pump twin	
Male/female	57%/43%
Malpresentation	29%
Major structural anomaly	9%
Hydramnios	46%
Congestive heart failure	53%
Previable	32%
Live-born	59%
Premature (<37 wk)	35%
Gestational age at delivery (wk)	29 ± 7
Birth weight (gm)	
Acardiac	651 ± 571
Pump-twin	1378 ± 1047

*Mean ± SD.

and analyzed with χ^2 with Yates' correction and the Student t test where appropriate. A p value of <0.05 was considered significant.

Results

Considering the entire data set, the mean maternal age was 26 ± 5.7 years (±SD). A total of 49% of the gravid women were primiparous; 46 of 49 cases (94%) involved twin gestation with two cases occurring in triplets and one in quadruplets.

The obstetric and neonatal course of 49 pregnancies with acardiac twinning is schematized in Fig. 1. One third of infants were delivered before viability was reached (25 weeks). Of the potentially viable pregnancies, 12% ended in pump-twin death in utero. In all, 12 of 49 (24%) were delivered live and mature, but they accounted for only 36% of the potentially viable pregnancies. Newborn intensive care unit admission was required in 41% of the pregnancies and 59% of those reaching viability. Five pump twins died in the neonatal period (10% overall; 17% of potentially salvageable infants), resulting in survival of only 24 pregnancies (50%).

Complications during pregnancy and the newborn period are summarized in Table I. One third of pregnancies resulted in spontaneous or voluntary abortion. Vaginal delivery was achieved in one third of the total, but more than half of potentially viable pregnancies required cesarean section. Transverse or breech positioning (33%) and fetal distress (30%) were major contributors to the high rate of operative delivery.

Hydramnios was a major maternal complication, occurring in 40% of all acardiac pregnancies. Hydramnios was associated strongly with preterm labor and pump-twin congestive heart failure. Eighty-two percent of patients with hydramnios experienced preterm labor requiring hospital admission and treatment, compared with a rate of 22% in pregnancies with normal amniotic fluid ($p < 0.01$). Similarly, excessive amniotic fluid was observed in 78% of pump twins with congestive heart failure, compared with 13% of those in whom congestive heart failure was not confirmed ($p < 0.001$).

Since hydramnios and pump-twin congestive heart failure were strongly associated with prematurity, the predictive ability of the twin weight ratio was compared to outcome. For all cases the twin weight ratio was 52% ± 8% (mean ± SEM). Fig. 2 illustrates the distribution of cases with and without pump-twin congestive heart failure with various values of the twin weight ratio. The mean twin weight ratio in cases of congestive heart failure was 88% ± 8.2% while the ratio in cases without congestive heart failure was only 21% ± 5% ($p < 0.0001$). Cases without pump-twin heart failure are clustered below twin weight ratio values of 80%.

The frequency of hydramnios with various twin weight ratios is tabulated in Fig. 3. The mean twin



Fig. 2. Acardiac/pump-twin weight ratio and occurrence of congestive heart failure in pump twin. *Open bars* are cases with pump-twin congestive heart failure. Weight ratio is acardiac weight expressed as percentage of pump-twin weight.

weight ratio for cases of hydramnios was 81% ± 8% versus 44% ± 9% in those without ($p < 0.005$). When the twin weight ratio was computed for pregnancies with and without preterm delivery (60% ± 2% vs 25% ± 2%) and neonatal intensive care unit admission (71% ± 3% vs 40% ± 2%), the relative size of the acardiac twins was highly predictive ($p < 0.001$).

Considering cases with twin weight ratios >50% (70% of cases), the frequency of hydramnios, pump-twin congestive heart failure, and prematurity was 44%, 25%, and 94% compared with 18%, 0%, and 35% when the ratio was less. The sensitivity, specificity, and predictive value of twin weight ratio >50% for selected outcome variables is presented in Table II. The sensitivity for detection of hydramnios and preterm delivery is above 80%. While the specificity and positive predictive power are statistically significant ($p < 0.05$), the values are modest (56% to 70%). With regard to twin weight ratio prediction of a live outcome, the sensitivity, specificity, and predictive power are all poor and not statistically significant.

Nevertheless, the risk of prematurity was linearly related to twin weight ratio. The week of delivery for each case is plotted against twin weight ratio in Fig. 4. The mean (±SD) gestational age at delivery was 29 ± 7.3 weeks, but premature deliveries tended to occur most frequently when the twin weight ratio was >60%. The negative slope of the regression line (Weeks at delivery = 37-6.9 × twin weight ratio) is statistically significant ($r = 0.57$; $p < 0.05$).

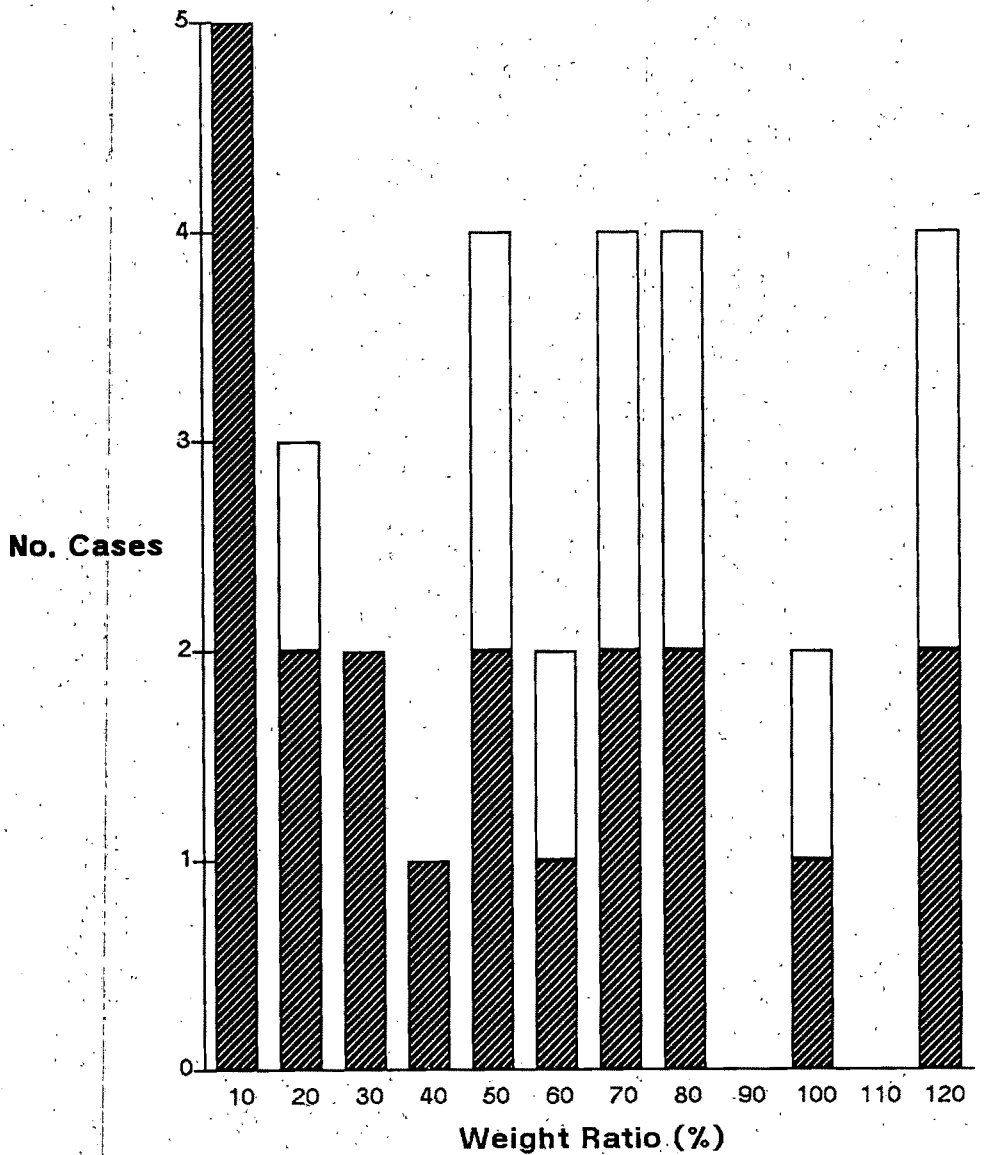


Fig. 3. Acardiac/pump-twin weight ratio and occurrence of hydramnios. Open bars are cases with hydramnios. Weight ratio is acardiac weight expressed as percentage of pump-twin weight.

Table II. Predictive value of twin-weight ratio > 50%

	*Hydramnios**	*Preterm delivery**	*Pump-twin death*
Sensitivity (%)	83	86	64
Specificity (%)	56	67	42
Positive predictive value (%)	56	71	45
Negative predictive value (%)	83	83	62

*$p < 0.05$.

Given the association of twin weight ratio and poor outcome, the problem of determining antenatally the weight of the acardiac twin was considered. The dimensions in this analysis. A second-order regression equation (Weight (gm) = $-1.66 \times$ Length $+ 1.21 \times$ Length^2) was computed and was predictive of acardiac weight with the use of its longest linear measurement ($r = 0.79$, $p < 0.001$, standard error of the estimate = 326 grams). When the actual and equation-predicted weights were compared, the mean error (±SE) in prediction was 240 ± 156 gm.

Comment

This study represents the largest single series of pregnancies complicated by acardiac twinning for which detailed perinatal outcome data are available. As such it provides a data base from which conclusions regarding outcome and the spectrum of perinatal morbidity in these pathologic pregnancies can be drawn.

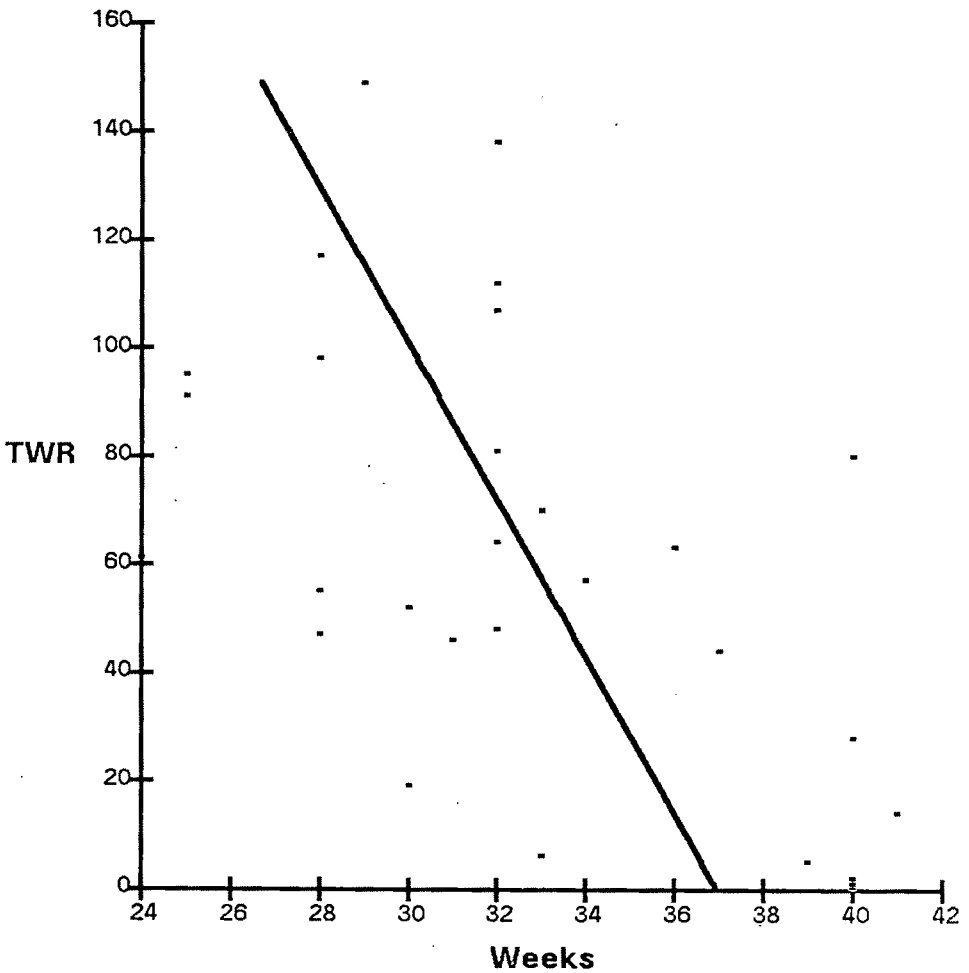


Fig. 4. Week of delivery and twin-weight ratio *(TWR). TWR* is acardiac weight expressed as percentage of pump-twin weight.

Frequently the acardiac fetus is mistaken for a twin who has died or an anencephalic fetus. The ultrasonographic features of absent head and trunk regions and increased soft tissue in the body aid in correct diagnosis.[5] Recently, pulsed Doppler examination has been used to show reversed flow through the umbilical artery of the acardiac twin.[6]

None of the acardiac pregnancies reported here underwent invasive therapies other than therapeutic amniocentesis in four cases. Thus the finding of 50% mortality provides a standard against which newer management schemes can be compared. The prominent role of hydramnios, pump-twin congestive heart failure and prematurity in the overall outcome agrees with previous reports.[6-9]

A new finding of this study was the relationship of acardiac size to pump-twin weight and its ability to predict outcome. Forecasting probable difficulties with hydramnios, preterm labor, and pump-twin cardiac decompensation may be useful in counseling patients in whom the diagnosis is made before the third trimester. Identifying a relatively small acardiac mass (<25% of normal-twin weight) may also help avoid invasive interventions such as selective hysterotomy[10] and acardiac umbilical ligation, occlusion or snaring,[7] since most of these are delivered near term.

In summary, this retrospective series suggests that half of acardiac pregnancies will result in fetal or neonatal death. Only a qurater can be expected to be delivered after 36 weeks. Preterm delivery and the attendant long-term morbidities can be expected for the remaining quarter. Innovations in management, pharmacologic treatment of the pump twin, or surgical interruption of acardiac umbilical flow may alter the prognosis in selective cases.

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Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats

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The effects of pentamidine isethionate on the developing embryo and fetus have not been previously published. Pregnant Sprague-Dawley rats were given various doses of pentamidine during the period of embryogenesis. Animals were killed on days 18 to 20 of pregnancy and their fetuses were removed by hysterectomy. Autopsies were performed on all fetuses. There were significant differences among groups with regard to maternal weight gain and pregnancy resorption. More pregnancy resorptions were noted in the group that received normal human doses (4 mg/kg/day) of pentamidine than in the control group ($p < 0.05$). One structural anomaly consisting of unilateral renal agenesis was noted in the 711 fetuses examined. Skeletal survey of fetal rats was unremarkable. Pentamidine was without teratogenic effects in rats when administered in doses similar to those recommended for adult humans; however, it appears to have an embryocidal effect when given in those same doses during embryogenesis. (Am J Obstet Gynecol 1990;163:912-6.)

Key words: Pentamidine, embryotoxic, teratogen, congenital anomaly

Because pregnant women with human immunodeficiency virus infection are at risk for *Pneumocystis carinii* pneumonia, pentamidine exposure for prophylaxis or treatment may be necessary. In addition, pregnant nursing personnel may be at risk for exposure while they are caring for patients with acquired immunodeficiency symdrome.[1] Pentamidine was first discovered and used in the 1930s and 1940s as an antiprotozoal agent.[2] During the 1950s pentamidine was first used to treat *P. carinii* pneumonia.[3] The Parasitic Disease Drug Service of the Centers for Disease Control supplied investigational pentamidine for the treatment of *P. carinii* pneumonia[4, 5] in 1967, and pentamidine was the most effective drug for this pulmonary infection until 1974. Trimethoprim-sulfamethoxazole at that time demonstrated activity against *P. carinii* in laboratory animals and soon replaced pentamidine as the primary treatment for *P. carinii* pneumonia.[6] However, pentamidine continued to be used as an alternative agent in those allergic to trimethoprim-sulfamethoxazole or in those who failed to respond. In 1984 LyphoMed, Inc. (Rosemont, Ill.) received Food and Drug Administration approval to market pentamidine isethionate as Pentam 300 for treatment of *P. carinii* pneumonia.[7]

This study was undertaken to evaluate the possible

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Table I. Resorptions in treatment groups compared with control group

Group	*Dams*	*Dose (mg/kg/day)*	*Days*	*Fetuses*	*Resorptions*	*p**
1	18	Control	6-11	207	14	—
2	14	4	6-11	151	26	0.02
3	18	20	6-8	196	6	0.18
4	16	20	9-11	157	9	0.89

*Compared with control group.

Table II. Hematocrit and blood glucose values in treatment groups compared with control group

Group	*n*	*Hematocrit (%) (mean ± SE)*	*p**	*Blood glucose (mg/dl) (mean ± SE)*	*p**
1	5	32.7 ± 1.95	—	60.6 ± 4.8	—
2	4	29.4 ± 6	0.59	57.0 ± 6.1	0.63
3	4	30.2 ± 1.9	0.36	71.8 ± 9.8	0.25
4	5	31.5 ± 1.8	0.62	72.2 ± 11.05	0.31

*Compared with control group.

teratogenicity and embryotoxicity of pentamidine because little information is available through animal studies or human experience. Reproductive studies have not been reported in the literature or performed by the product manufacturer.[7]

Material and methods

Sprague-Dawley rats initially derived from the ARS/Sprague-Dawley colony in Madison, Wisconsin, were used. Female rats weighing 250 gm and male rats weighing 300 gm were purchased and permitted to acclimate for 1 week after arrival. The rats were housed in controlled lighting (lights on between 6 AM and 6 PM) and temperature (24° to 26° C) conditions. Laboratory chow and tap water were freely available. Four to five rats were housed per cage. The animals were mated when the female rat was determined to be in proestrus or estrus by appropriate cytologic changes noted in the vaginal fluid.[8] Eighteen to 24 hours after the male and female rats were placed together, presence or absence of sperm was determined by evaluation of vaginal secretions under light microscopy. If sperm were present, the day of gestation was assigned as zero. As female rats demonstrated sperm positivity, they were randomly assigned to either the control group (group 1) or three different pentamidine groups: 4 mg/kg/day on days 6 through 11 (group 2), 20 mg/kg/day on days 6 through 8 (group 3), or 20 mg/kg/day on days 9 through 11 (group 4) (Table I). The treatment periods were chosen on the basis of implantation of the blastocyst (day 6) and early organogenesis (days 7 through 11).[8] Pentamidine (Pentam 300,2 mg/ml) was administered via tail vein injection. In a previous experiment (unpublished observations) 40% of pregnant rats died after tail vein injection of 40 mg/kg of pentamidine. In light of these data the high-dose groups in this study were chosen to receive 20 mg/kg/day (groups 3 and 4). The control group received the same volume of saline solution only as group 2. The accepted adult human dose of pentamidine is 4 mg/kg/day.

During pregnancy the rats were handled only for dosing and daily weighing. On days 18 to 20 of pregnancy (normal gestation, 20 to 22 days), the dams were killed either by guillotine or with ether, and cesarean section was performed immediately. Blood was obtained from randomly selected animals in each group for hematocrit and blood glucose determination (Table II). The fetuses were counted and the uteri were examined for evidence of embryo resorption. The fetuses were immediately placed in 10% formalin.

A skeletal survey of posteroanterior and lateral views of each fetus was performed. A xeroradiographic technique was used with selenium plates and power settings for the posteroanterior view of 120 mA at 40 to 45 kilovolt peak and 100 mA at 40 kV(p) for the lateral views. Films were evaluated for cranial, rib, vertebral, or long bone abnormalities.

After a thorough external examination of the fetuses, autopsies were performed under the magnification of a dissecting microscope. Autopsies included visualization and evaluation of palate, heart and major vessels, lungs, liver, kidneys, ureters, and bladder. Statistical analysis included the use of χ^2, Student t test, and analysis of variance.

Results

In this study 711 fetal rats were evaluated. The detailed external examinations revealed no obvious neural tube defects, limb reduction deformities, or anterior

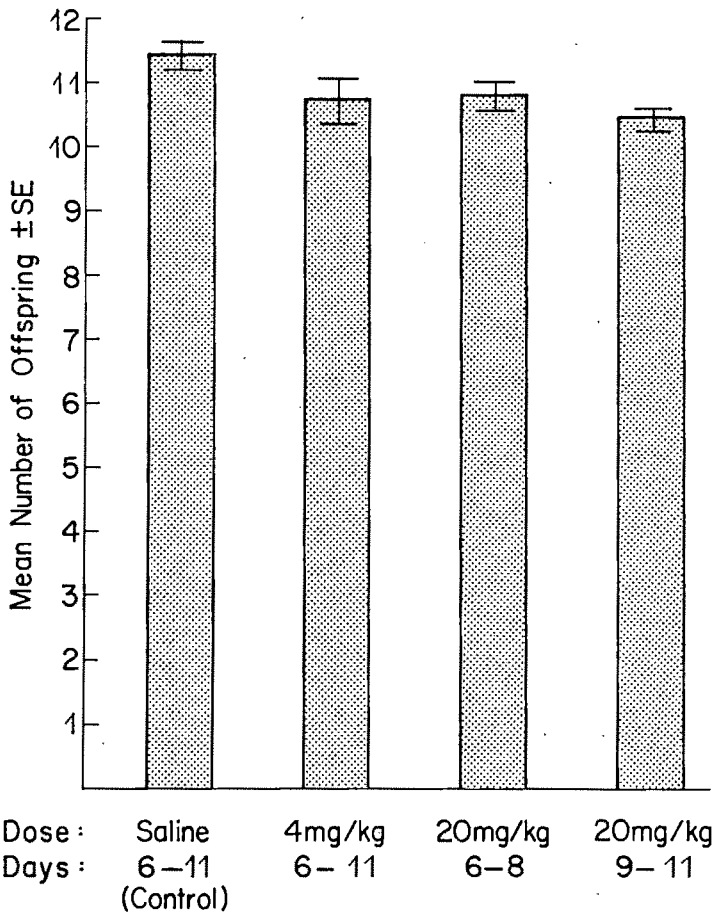


Fig. 1. Mean (± SE) number of offspring per litter. Control versus pentamidine treatment groups.

abdominal wall adnormalities. The necropsy of fetal rats revealed no detectable major anomalies except for one case of unilateral renal agenesis in group 2. Skeletal surveys of the fetal rats were unremarkable with regard to vertebral column, ribs, or long bone deformities. Comparison between groups revealed more resorptions in group 2 ($n = 26$) than in the control group ($n = 14$); this difference was significant ($p = 0.02$) (Table I). Litter size was not significantly different between the groups (Fig. 1). Other differences between groups included dam weight gain (Fig. 2). The weight at death in the control group was significantly greater than in group 4 ($p = 0.038$). Three other dams in groups 3 and 4 developed severe constipation with obvious fecal impaction at death.

During the experiment complications encountered with the administration of pentamidine included deaths of three dams that received higher doses of pentamidine. Death was preceded by lethargy, unresponsiveness, and faintly palpable heartbeat. These observations are consistent with those effects of pentamidine in rats as reported by Bielenberg and Krieglstein.[9] Pentamidine appears to have not only a peripheral hypotensive action but also a cardiac effect, including decreased heart rate and myocardial contractility.[9] Death has been reported in humans as a complication of pentamidine therapy.[8] Systemic complications with pentamidine administration were not noted in the dams in group 2 (dose of 4 mg/kg/day).

It has been reported that pentamidine may be toxic to rat islet cells in vivo and in vitro.[10] However, the mesylate salt as opposed to the isethionate salt was noted to be more potent in suppression of beta cell function. In addition to β-cell toxicity, pentamidine, through the possible mechanism of dihydrofolate reductase inhibition, may cause anemia. Blood glucose and hematocrit values obtained at death from randomly selected subjects from each group were not significantly different between groups (Table II). Whether these measurements are a sensitive indication of toxicity is unknown; histologic examination of the pancreata was not done.

Comment

Pentamidine [4,4'-diaminodiphenoxypentane di-(β-hydroxyethansulfonate)] is structurally related to guanidine. Pentamidine is made available as the isethionate salt and is active against the protozoan par-

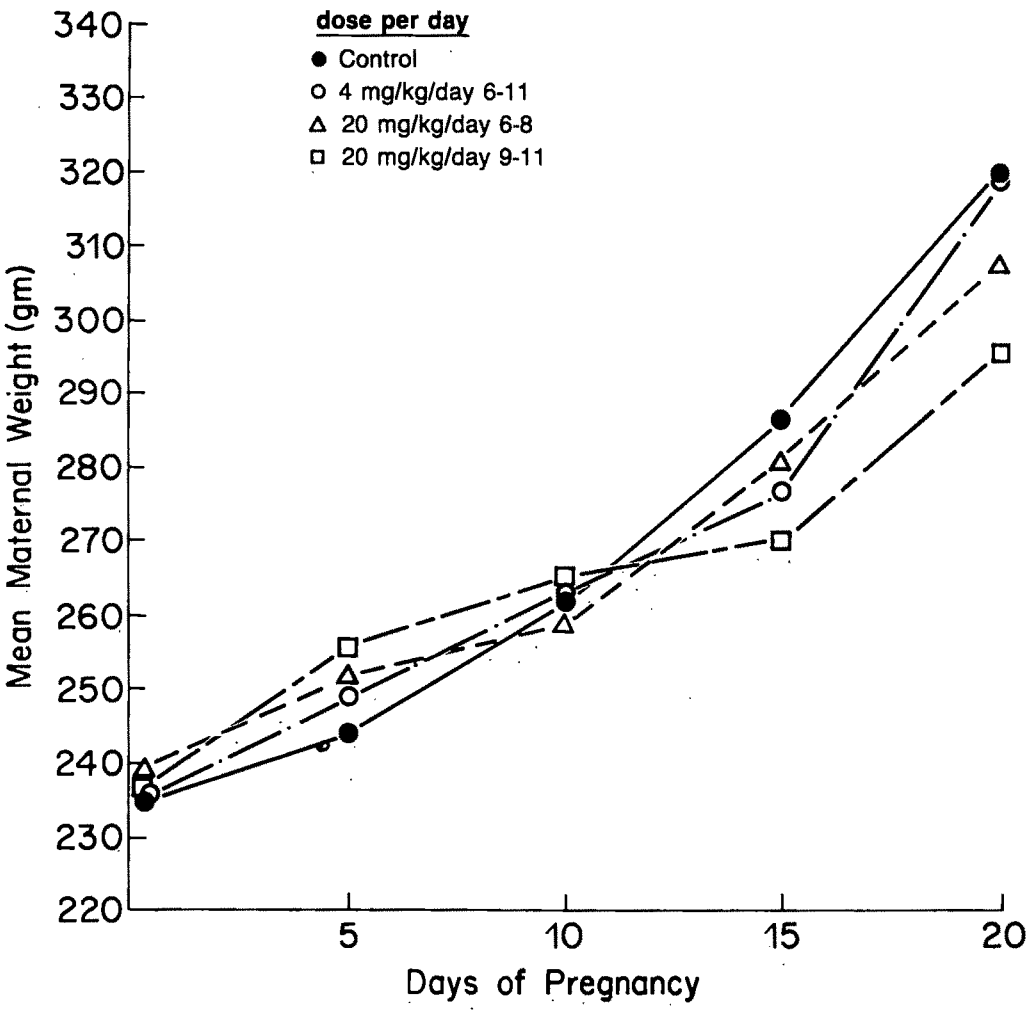


Fig. 2. Mean maternal weight versus day of pregnancy for three treatment groups and control group.

asite *P. carinii*.[2] The mechanism of action for pentamidine has been proposed to include inhibition of dihydrofolate reductase, interference with aerobic glycolysis, or inhibition of oxidative phosphorylation and nucleic acid synthesis.[11]

Pharmacokinetically, pentamidine has been studied in mice,[12] rats,[13] and humans with malignant disease[12] and acquired immunodeficiency syndrome.[14] In mice, peak levels after peritoneal injection were noted in kidneys, with next highest levels in the liver. No pentamidine was found in brain tissue. Excretion occurred primarily through the kidneys and to a smaller degree through the gut; in both routes the drug was unchanged.[15] In rat studies similar distribution of the drug was noted with parenteral administration. However, much lower systemic levels were noted with the aerosolized route.[13] In humans a parenteral dose of 4 mg/kg/day given for 12 days resulted in peak plasma values at 1 hour after injection. A mean of 17% of the 4 mg/kg dose was excreted unchanged in the 24-hour period after administration. Drug could be detected unchanged in urine at 8 weeks after treatment ceased.[12]

Pentamidine has been reported to cross the human placenta as determined in the in vitro explanted perfused human cotyledon in low concentration.[15] In our experience pentamidine administered to dams on day 18 of gestation (40 mg/kg) revealed a maternal/fetal gradient of 18:1 at 8 hours after injection as detected by high-pressure liquid chromatography[15] (maternal serum, 5.6 μg/ml; placenta, 0.94 μg/gm; fetal liver, 0.32 μg/gm), indicating fetal exposure similar to that in the in vitro human placenta (unpublished observations).

Pentamidine was not teratogenic in the rat model we used. However, there were more pregnancy resorptions in the group that received normal human doses of pentamidine on days 6 through 11 of gestation. It is conceivable that some early embryo losses may be related to malformations that were lethal to the conceptus. Although higher doses of pentamidine (20 mg/kg/day) were administered at critical times during gestation, these were for a shorter duration and were not asso-

ciated with higher resorption rates. It would thus appear that lower doses of sustained administration of pentamidine may have ill effects, possibly because of slow excretion rates and tissue accumulation.

The results of this study suggest that pentamidine has an embryocidal effect when administered parenterally over a sustained period of time. Lower tissue levels may be achieved with aerosolized administration.[18]

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An evaluation of the chorionic villus sampling learning curve

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Prior studies have identified a correlation between the rate of fetal loss (subsequent to chorionic villus sampling) and the operators's level of experience. However, centers performing only modest numbers of procedures during the initial phase of their programs have reported loss rates similar to those of the more active diagnostic units. Our personal experience would suggest that a "learning curve" for chorionic villus sampling does exist but that fetal loss may be an insensitive end point with which to evaluate the impact of cumulative performance. In an attempt to quantify the learning curve that we have appreciated subjectively, a detailed analysis of our initial experience with chorionic villus sampling was undertaken. Between May 1988 and August 1989, a total of 185 procedures were accomplished consecutively by one operator and form the basis for this analysis. Transcervical (n = 82) and transabdominal (n = 103) techniques were used for posterior and anterior-fundal placental locations, respectively. Three pregnancy losses occurred and insufficient material for analysis was retrieved in five patients. We observed a significant reduction in the required number of placental aspirations during the study interval ($p < 0.001$). When analyzed separately, consecutive performances of the transabdominal technique demonstrated a significant reduction in the mean number of placental passes ($p < 0.00001$) along with more efficient sampling (increased sample weight/aspiration attempt; $p < 0.01$). Although the fetal loss rate is a critical measure of safety and may directly be related to operator experience, other measures of expertise (e.g., single-pass success rate) may be more appropriate indicators of competence and may be useful to centers wishing to initiate their own chorionic villus sampling programs. (Am J Obstet Gynecol 1990;163:917-22.)

Key words: Chorionic villus sampling, learning curve, transcervical, transabdominal

The current trend in prenatal diagnosis appears to favor an increased application of first-trimester procedures, including early amniocentesis and chorionic villus sampling (CVS). As the demand for CVS grows, more perinatal centers will undoubtedly offer this alternative procedure. Prior studies have identified a correlation between the rate of fetal loss after CVS and the operator's level of experience.[1-3] Other centers performing fewer procedures have reported fetal loss rates similar to those of the more active and established diagnostic units.[4, 5] The multiinstitutional CVS trial reported by Rhoads et al.[6] did not directly address the impact of operator expertise but did identify an increased fetal loss rate among patients requiring multiple placental aspirations. Inasmuch as that study relied exclusively on transcervical sampling, fundal placentation (rather than inexperience) may have been partly responsible for the increased number of sampling attempts and corresponding pregnancy losses.

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Since beginning our CVS program, we have appreciated a subjective "learning curve," despite the fact that our initial and subsequent loss rates have been low. Unlike most other centers, we have used both transcervical and transabdominal sampling from the inception of our program, selecting the preferred approach on the basis of placental location.[7] It is our impression that the fetal loss rate may be an insensitive end point with which to evaluate the impact of cumulative performance. Moreover, since the absolute number of fetal losses in any center's initial experience is small,[4] it is difficult to avoid a type II statistical error in analyzing any correlation with pregnancy outcome.

To identify objective evidence of the CVS learning curve that has been appreciated subjectively, we undertook a detailed evaluation of a single operator's initial experience with both transabdominal and transcervical techniques. With this analysis we hoped to estimate the number of procedures required to achieve competence or at least identify indicators of operator improvement over time. These indicators could then be used prospectively by centers wishing to develop and monitor their CVS programs.

Material and methods

The 185 cases in this study represent a subset of the 252 CVS procedures performed during the initial 16

Table I. Selected patient characteristics during four study intervals

Variable	Interval of study			
	1988		1989	
	May-Aug. (N = 48)	Sept.-Dec. (N = 54)	Jan.-April (N = 42)	May-Aug. (N = 41)
Indications				
Advanced maternal age (No.)	38 (79.2%)	48 (88.9%)	40 (95.2%)	38 (92.7%)
Prior aneuploidy (No.)	3 (6.3%)	2 (3.7%)	0 (0%)	1 (2.4%)
Other (No.)	7 (14.5%)	4 (7.4%)	2 (4.8%)	2 (4.9%)
Prior fetal loss (No.)	14 (29.2%)	19 (35.2%)	10 (23.8%)	12 (29.3%)
First-trimester bleeding (No.)	9 (18.8%)	10 (18.5%)	12 (28.6%)	6 (14.6%)
Gestational age at CVS (wk, mean ± SD)	10.4 ± 1.2	10.3 ± 1.1	10.1 ± 1.3	10.3 ± 1.2

months of our program (May 1988 to August 1989). These cases were selected for analysis because they were performed consecutively by a single operator. Twin samplings ($N = 10$ sets) and the concurrent cases of a second operator ($N = 47$) were excluded. Procedures were performed between 8 and 12 weeks' gestation. Informed consent was obtained in all instances and emphasized the concept that selection of either the transabdominal or transcervical approach was primarily dependent on placental location. This protocol was approved by the institutional review board of the hospital.

Transcervical sampling was used in those patients with either low placental implantation (directly covering the internal cervical os) or posterior placental location. In contrast, transabdominal CVS was used in those patients with either an anterior or a fundal placenta. Uterine position and maternal factors (e.g., obesity) were also considered when selecting the sampling method. Simultaneous ultrasound imaging was provided by a 3.5 MHz sector transducer (Ultramark 4, Advanced Technology Laboratories, Inc., Bothell, Wash.). A self-assembled 5.8 Fr, 27 cm polyethylene catheter (Cook Urological Inc., Spencer, Ind.) was used in all transcervical procedures. If required, a new catheter was used for each placental pass. A coaxial needle system was used in transabdominal procedures, consisting of an 18-gauge, 15 cm, thin-walled outer guide needle and a 20-gauge, 20 cm sampling needle. Thirty milliliter syringes were used for both procedures and up to three placental aspirations were allowed per patient. The sampling objective was to obtain adequate tissue (≥10 mg) for both direct preparation and culture, but the decision to attempt repeat aspirations (if a lesser sample was obtained) was at the discretion of the operator. The cytogeneticist verified the presence of villus tissue and estimated sample weight on the basis of established photographic standards.

Patient follow-up included phone contact within 1 week of the procedure, repeat ultrasound evaluation in the midtrimester, and written confirmation of pregnancy outcome by the referring obstetrician.

Statistical analysis of the data was accomplished by means of analysis of variance for continuous measures along with χ^2 (2×2 comparisons) and contingency tables (multiple column-row comparisons) for discrete parameters. Significance was considered at $p < 0.05$.

Results

To appreciate trends over the 16-month study period, patients were grouped into 4-month subsets. Selected patient characteristics during the study intervals are shown in Table I. A history of one or more spontaneous losses was common (29.7%) as was bleeding in the first trimester (20%). All patients meeting gestational age criteria underwent sampling with the exception of those patients who were first seen with either a nonviable pregnancy or active bleeding on the scheduled day of testing. Initially, transcervical CVS was used most often but was replaced by more frequent transabdominal procedures in the later months of the study (Table II; $p < 0.001$). Because there was no difference in the distribution of placental location or uterine position over time, this finding most likely represents development of operator preference for transabdominal CVS in those cases accessible by either route of sampling.

Procedure-related variables that may be representative of enhanced expertise over time are shown in Table II. A decline in the required number of placental aspirations was observed, such that 88% of all patients required only a single pass by the last 4-month interval (Fig. 1). A parallel decline in the proportion of patients requiring three samplings was also observed (16/48 between May and August 1988 vs 0/41 between May and August 1989; $p < 0.001$). A trend of decreasing aggregate sample weight was noted ($p = 0.057$), but no difference in the sample weight per aspiration attempt was seen. Inability to obtain a sample was uncommon (5 of 185 patients).

These same procedure-related variables were analyzed separately for the transcervical and transabdominal subsets (Tables III and IV). In transcervical subsets

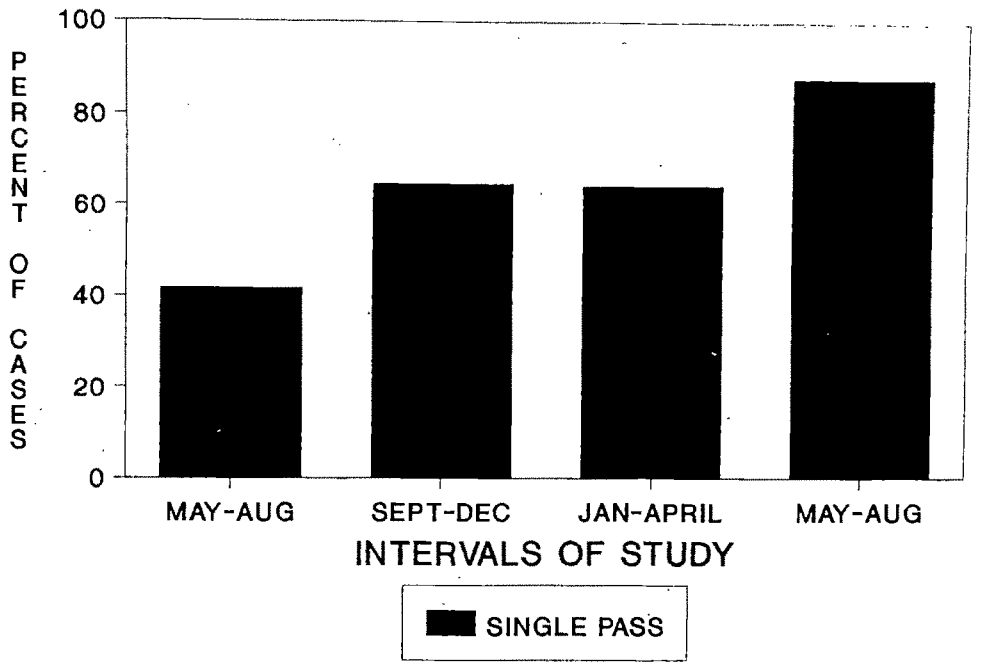


Fig. 1. Proportion of CVS procedures accomplished in a single aspiration correlated with increasing experience during study intervals ($p < 0.0005$).

Table II. Procedure-related variables during four study intervals

	Interval of study			
	1988		*1989*	
Variable	*May-Aug. (N = 48)*	*Sept.-Dec. (N = 54)*	*Jan.-April (N = 42)*	*May-Aug. (N = 41)*
Transabdominal/transcervical ratio*	14/34	30/24	30/12	29/12
Placental aspirations† (No., mean ± SD)	1.9 ± 0.9	1.4 ± 0.6	1.5 ± 0.7	1.1 ± 0.3
Aggregate weight (mg, mean ± SD)	23.2 ± 11.5	21.3 ± 8.5	19.3 ± 9.8	17.9 ± 8.6
Aggregate weight < 10 mg (No.)	5 (10.4%)	1 (1.8%)	4 (9.5%)	3 (7.3%)
No sample obtained (No.)	3 (6.3%)	0 (0%)	1 (2.4%)	1 (2.4%)

*χ^2; $p < 0.001$

†Analysis of variance; $p < 0.0001$; differences are significant after Bonferroni adjustment.

successful sampling was accomplished with a single pass in 11 of 12 patients during the final four-month period compared to 17 of 34 patients in the initial four-month period. Improvement in the transabdominal technique over time was represented by a significant reduction in the number of required sampling attempts, as well as a significant increase in the amount of villi retrieved per placental aspiration.

Three fetal losses occurred (before 20 weeks' gestation; patients 10, 62, and 64). Although it is notable that these fetal losses occurred "early" in the study (during the first 5 months), the significance of this observation is unclear. In an attempt to identify lesser morbidities that might also relate to proficiency in sampling, we analyzed the incidence of postprocedure bleeding (within 48 hours) over the duration of the study (Fig. 2). A nonsignificant trend toward a reduction in this complication was observed; however, most bleeding was associated with the transcervical technique (11 of 15 patients), and 10 of these patients also had a history of bleeding before the procedure.

Comment

During the initial 16 months of this experience with CVS, we observed trends that support the concept of a learning curve. Specifically, fewer placental aspirations were required overall; a larger sample size and more effective sampling was noted with the transabdominal technique and less postprocedure bleeding was reported among the transcervical procedure subset. The low rate of fetal loss during the entire study interval, although encouraging, belied the fact that improvement in technique and efficiency was still taking place. Unlike other centers that have reported an ex-

Table III. Procedure-related variables during four study intervals: Transcervical cases

Variable	*Interval of study*			
	1988		*1989*	
	May-Aug. (N = 34)	*Sept.-Dec. (N = 24)*	*Jan.-April (N = 12)*	*May-Aug. (N = 12)*
Placental aspirations (No., mean ± SD)	1.7 ± 0.8	1.3 ± 0.5	1.5 ± 0.8	1.1 ± 0.3
Single aspiration only (No.)	17 (50.0%)	18 (75.0%)	8 (66.7%)	11 (91.7%)
Three aspirations required (No.)	6 (17.6%)	1 (4.2%)	2 (16.7%)	0 (%)
Aggregate weight (mg, mean ± SD)	27.1 ± 10.6	25.8 ± 9.8	26.3 ± 10.2	18.8 ± 10.8
Sample weight/aspirate (mg, mean ± SD)	20.7 ± 11.8	23.9 ± 11.7	23.7 ± 13.4	18.5 ± 10.7

χ^2 and analysis of variance as appropriate; no significant differences noted after Bonferroni adjustments for multiple comparisons.

Table IV. Procedure-related variables during four study intervals: Transabdominal cases

Variable	*Interval of study*				
	1988		*1989*		
	May-Aug. (N = 14)	*Sept.-Dec. (N = 30)*	*Jan.-April (N = 30)*	*May-Aug. (N = 29)*	*p*
Placental aspirations (No., mean ± SD)	2.5 ± 0.8	1.5 ± 0.6	1.5 ± 0.7	1.1 ± 0.3	<0.00001
Single aspiration only (No.)	3 (21.4%)	17 (56.7%)	19 (63.3%)	25 (86.2%)	<0.001
Three aspirations required (No.)	10 (71.4%)	1 (3.3%)	3 (10.0%)	0 (0%)	<0.000001
Aggregate weight (mg, mean ± SD)	13.9 ± 7.6	17.8 ± 5.1	16.6 ± 8.1	17.6 ± 7.6	NS
Weight/aspiration (mg, mean ± SD)	7.5 ± 7.0	13.3 ± 4.7	13.8 ± 9.3	16.4 ± 8.0	<0.01
Single guide-needle pass (No.)	11 (78.6%)	25 (83.3%)	23 (76.7%)	26 (89.6%)	NS

χ^2 and analysis of variance as appropriate; Bonferroni adjustments for multiple comparisons. NS, not significant.

tensive "preparatory experience" with pregnancies scheduled for elective termination,[4, 5] fewer than 20 cases were logged in our center before CVS was performed on continuing pregnancies (primarily because of limited local availability of termination services).

Our study was restricted to the experience of a single operator so that we might accurately represent the learning curve for an individual, since it is likely to be different from one operator to another. Differences in expertise among centers has also been alluded to both by the variation in reported fetal loss rates[8] and recently by a wide range (among seven centers) in the proportion of cases requiring multiple placental passes (7% to 45%).[6] The second operator in our center has also experienced a learning curve, although fewer cases have been required to reach a consistent (>90%) single-pass rate. This may relate to a prior extensive experience with ultrasound-guided perinatal procedures.[9] As an extension of these observations, it may be appropriate to have only one operator at a time learn these techniques, especially if a limited initial caseload is anticipated.

When CVS was initiated in our center, we were not committed to either the transcervical or transabdominal approach. However, our preparatory experience suggested that posterior or low implantations were most easily sampled transcervically, whereas fundal and anterior placentas were more amenable to transabdominal aspiration. During the latter portion of this study, those cases amenable to either approach were most

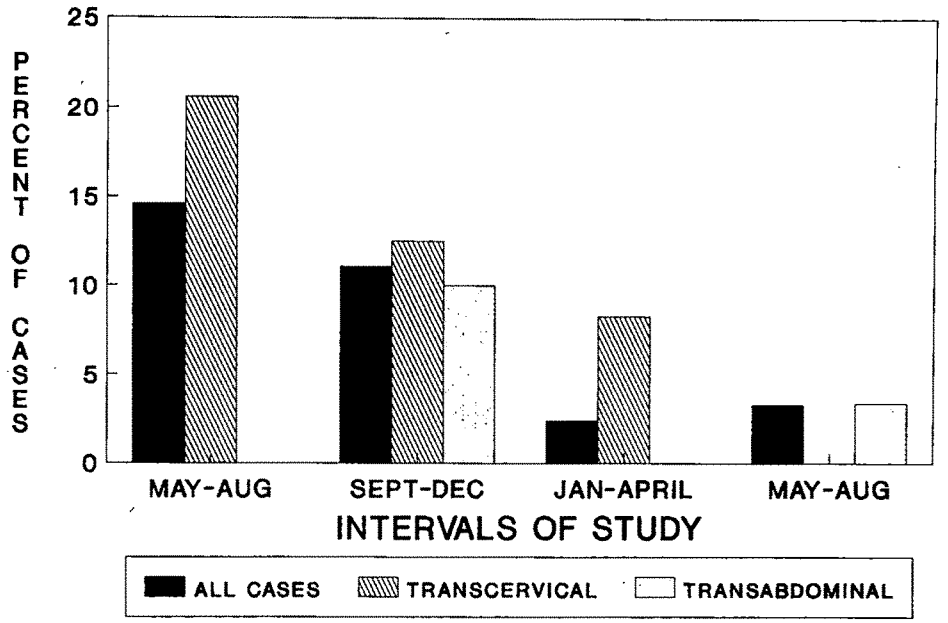


Fig. 2. Incidence of postprocedure bleeding (within 48 hours) compared by route of sampling and correlated with increasing experience during study intervals ($p = 0.07$). Bleeding did not occur during interval if subgroup is not represented by *shaded bar*.

often sampled transabdominally. This shift favoring transabdominal procedures likely contributed to the temporal improvement observed (Table IV). The virtues of transabdominal sampling have been identified by others[10, 11] and include avoidance of cervicovaginal bacteria and less frequent postprocedure bleeding. However, until a properly controlled trial (which includes placental location and uterine anatomy as independent variables) identifies a safer approach, we believe that both procedures should be learned and used.

Obstetricians are generally familiar with percutaneous procedures and experience with ultrasonographic guidance should provide an additional advantage in learning transabdominal CVS. It is therefore interesting that more dramatic improvements seemed to occur when the transabdominal procedure was performed in this series. We would suggest that whether a single or coaxial needle system is used matters less than the angle with which the chorion frondosum is entered.[11, 12] Entry parallel to the long axis of the placenta is of great importance to both the success of the sampling and the amount of tissue retrieved, especially when a small-gauge needle is used. These nuances in transabdominal technique probably contributed most to the learning curve we observed.

Review of these data has not identified an obvious "break point" beyond which CVS competence was achieved. A more sophisticated analysis, combining various end points indicative of expertise, would only serve to characterize the experience of a single physician. Instead factors such as a minimum "single-pass success rate" should probably be emphasized.[6] This is likely to vary somewhat, depending on inherent operator skill and prior experience. It is reassuring to note that during our acquisition of expertise and that of others[4] an increase in fetal loss rate was not realized. Hopefully this pattern will continue as more perinatologists offer these services to their patients.

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The association of single umbilical artery with cytogenetically abnormal pregnancies

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The clinical significance of the absence of one of the two umbilical arteries (single umbilical artery) lies in its association with congenital malformations. Whether this association includes cytogenetic abnormalities is less clear. A retrospective review of all detected chromosomally abnormal pregnancies at the University of Maryland was carried out. Of 109 cytogenetically abnormal pregnancies, the number of umbilical cord vessels could be documented in 53 cases. Six (11.3%) had a single umbilical artery. A single umbilical artery was noted in two of nine fetuses (22.2%) with trisomy 18 and in two of six fetuses (33.3%) with trisomy 13. Two other unusual chromosomal constitutions were noted in cases of a single umbilical artery. None of the 11 fetuses with sex chromosome abnormalities (including eight with monosomy X) had a single umbilical artery. Of 18 fetuses with trisomy 21, none had a single umbilical artery. This study suggests that a single umbilical artery is preferentially associated with certain karyotypic abnormalities and that trisomy 21 does not appear to be associated with a single umbilical artery. (AM J OBSTET GYNECOL 1990;163:922-5.)

Key words: Single umbilical artery, chromosome abnormality, trisomy

A normal umbilical cord contains a single vein and two arteries surrounded by Wharton's jelly. It has been recognized for centuries that on occasion abnormalities of the umbilical cord may be seen. One of the most common of these abnormalities with clinical significance is that of a single umbilical artery. A single umbilical artery represents the absence of the second umbilical artery and its importance has been discussed for many years. The first recorded accounts of a single umbilical artery date from the 1500s.[1] The first account in the American literature is in 1908.[2] The clinical significance of a single umbilical artery lies in its association with congenital malformations. A variety of malformations have been associated with a single umbilical artery, including cardiovascular malformations, central nervous system defects, gastrointestinal defects, musculoskeletal malformations, and urogenital defects.[1, 3, 4]

Much of the literature on single umbilical artery predates the clinical use of chromosome analysis, and it is difficult to find information concerning the association of a single umbilical artery with chromosomal abnormalities in the literature.[4] Several of the early descriptions of autosomal trisomies describe a single umbilical artery as an occasional feature in anecdotal cases; however, precise incidences are not available.[5]

Material and methods

In an effort to delineate a possible association between the presence of a single umbilical artery and aneuploidy, a retrospective study of all cytogenetically abnormal pregnancies or deliveries was carried out.

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These pregnancies were ascertained through the cytogenetic laboratory at the University of Maryland Hospital. All abnormal karyotypes obtained between 1982 and May 1989 were evaluated. Cases included for evaluation were both amniocentesis specimens and tissue culture specimens (of second- and third-trimester pregnancies). Because of the lack of available information or appropriateness, cases excluded from further evaluation were those with aneuploidy identified from any first-trimester specimens (such as abortus material and chorionic villus samples), anembryonic molar pregnancies, and neonatal blood and bone marrow specimens. Both laboratory and clinical records were reviewed in an effort to find descriptions of the types of anatomic changes that were associated with the cytogenetic abnormality, as well as pathologic conditions in the placenta or autopsy documentation of pathologic conditions in the placenta and umbilical cord. Records from several hospitals were obtained. All records were reviewed by D. N. S.

Results

Data from amniocentesis and tissue culture specimens were initially evaluated separately because of inherent differences between the groups in gestational age and severity of morphologic abnormalities.

A total of 80 amniocentesis specimens were ascertained with abnormal karyotypes. These were mainly second-trimester gestations (75 of the 80 cases), most of which were first seen because of an indication of advanced maternal age (55 of the 80 cases). Although sonographically detected morphologic abnormalities were noted in several instances, this was the initial indication for amniocentesis in only 15 of the 80 cases. None of the patients carried the prenatal diagnosis of a single umbilical artery, and therefore awareness of its presence was not an indication for amniocentesis and did not affect clinical management in any instance. Of the 80 karyotypically abnormal amniocentesis specimens, pathologic follow-up could be obtained in only 36 cases. Documentation of the pathologic status of the remaining 44 cases was unattainable for one of several reasons. Four patients carried the pregnancy to term despite the knowledge of aneuploidy. The records from the referring institution where the specimen originated were not available in 27 cases. The pathology report did not comment on the number of umbilical vessels in nine cases (six of which were specimens from dilatation and evacuation procedures). One patient refused autopsy examination and three in-house charts were unavailable. The 36 cases with pathologic documentation included 13 with trisomy 21, seven with trisomy 18, four with trisomy 13, four with monosomy X, and eight with unusual karyotypes listed in Table I. In 33 of these 36 cases the gestational age was 28 weeks or less. Of these 36 cases, five had a single umbilical artery. These included two with trisomy 18 (out of seven in which follow-up was obtained) and one with trisomy 13 (out of four in which follow-up was obtained). Additionally there were two single umbilical arteries noted in unusual cytogenetic abnormalities—a deletion of the short arm of chromosome 5 [46,XX,del(5)(qter→p14:)] and a case of trisomy 9 mosaicism [46,XX/47,XX+9].

Table I. Amniocentesis

Karyotype	*No. with available pathologic documentation*	*No. with single umbilical artery*	*%*
Trisomy 21	13	0	0
Trisomy 18	7	2	28.6
Trisomy 13	4	1	25
Triploidy	0	—	—
Monosomy X	4	0	0
Other sex*	3	0	0
Other†	5	2	40
Total	36	5	13.9

*Other sex karyotypes included: 47,XXX; 47,XXY; 45,X/46, X+mar.

†Other karyotypes included: 46,XX,del (5) (qter→p14:)
46,XX/47,XX+9
46,XY,17q+
46,XX,inv(1)(p21p36),del(1)(p22.1→p22.3?)
46,XX,t(1;19)(p11;p11)/47,XX,t(1;19)(p11;p11)+der(1)t(1;19)(p11;p11)

Twenty-nine other patients, after being informed of the presence of an ultrasonographically detected morphologic abnormality or a fetal death, declined prenatal diagnosis of karyotype. In these cases fetal tissues or placental villi were obtained at the time of discontinuation of the pregnancy and sent to the cytogenetic laboratory for karyotyping. This group included a wider range of gestational ages but mainly pregnancies in the second trimester (15 of 29 cases at ≤28 weeks). All patients in this group, for whom termination of pregnancy was an available option, proceeded with termination. This group included nine cases of fetal death and five sonographically detected morphologic abnormalities at or near term. Of these 29 specimens, pathologic follow-up could be obtained in 17 cases (12 of which were ≤28 weeks' gestation). The 12 cases without pathologic follow-up included nine in which the charts were not available at the referring institutions and three in which the charts were not available within the University Hospital. These 17 cases included five with trisomy 21, two with trisomy 18, two with trisomy 13, four with triploidy, and four with monosomy X (Table II). Of these 17 cases, only one (with trisomy 13) was noted to have a single umbilical artery.

In total, 109 aneuploid pregnancies were identified and complete pathologic follow-up was obtained in 53 (48.6%). Of these 53 cases, six (11.3%) were associated

Table II. Fibroblast cultures

Karyotype	*No. with available pathologic documentation*	*No. with single umbilical artery*	*%*
Trisomy 21	5	0	0
Trisomy 18	2	0	0
Trisomy 13	2	1	50
Triploidy	4	0	0
Monsomy X	4	0	0
Total	17	1	5.9

Table III. Karyotypes found in association with single umbilical artery

Karyotype	*No.*
47,XY,+13	2
47,XX,+18	2
46,XX,del(5)(qter→p14:)	1
46,XX/47,XX,+9	1

with a single umbilical artery (Table III). If the data from trisomy 13 and trisomy 18 pregnancies are combined, 4 of 15 pregnancies (26.7%) demonstrated a single umbilical artery. This, when compared with 0 of 18 trisomy 21 pregnancies demonstrating a single umbilical artery, reaches statistical significance (two-tailed Fisher's exact test, $p = 0.033$).

Comment

Single umbilical artery is a relatively common congenital malformation the incidence of which ranges between 0.08% and 1.9% with a mean of 0.63%.[1] Data obtained from live births show a lower incidence than those obtained from stillbirths, and the incidence of a single umbilical artery in first- and second-trimester fetuses is still higher, ranging from 0.2% to 9.68%.[1, 4] Other factors that have been associated with an increased incidence of a single umbilical artery in addition to congenital malformations include white race and low birth weight.[1, 6] Multiple gestation, especially with discordance in weight, has also been associated with a single umbilical artery.[1, 7]

It has been suggested that a single umbilical artery is associated with cytogenetic abnormalities and with congenital malformations in general.[4] Data supporting this are difficult to find and specific associations with individual chromosome abnormalities are not well documented in the literature. A single umbilical artery has been found in 10% to 50% of infants with trisomy 18.[8] Smith[5] suggested that single umbilical artery is on occasion associated with trisomy 13. In a report of 107 fetuses with central nervous system malformations, 20 (18%) had a single umbilical artery.[9] Fifteen of these 20 were karyotyped and eight (53%) were aneuploid (trisomy 13 or trisomy 18). Of karyotyped fetuses without a single umbilical artery in this same series, 11 of 45 (24%) were aneuploid. To our knowledge there are no other reports (other than anecdotal case reports) of any other chromosomal abnormalities (including trisomy 21) in association with a single umbilical artery. In this small retrospective study, out of a total of 109 cytogenetically abnormal pregnancies, pathologic data could be obtained in 53 cases. A total of six pregnancies were noted to have a single umbilical artery. This gives an incidence of 11.3% for single umbilical arteries among cytogenetically abnormal pregnancies in general. Additionally it appears that specific cytogenetic abnormalities are associated with a single umbilical artery. Of the six cases of single umbilical artery found, two were in cases of trisomy 18 (two of nine, 22.2%) and two were in cases of trisomy 13 (two of six, 33.3%). It is difficult to interpret the significance of the other two cases with a single umbilical artery (46,XX/47,XX+9; 46,XX,5p−).

In this series there is no association of a single umbilical artery with trisomy 21. Of 18 cases of trisomy 21 in which pathologic follow-up data were obtained, none demonstrated a single umbilical artery. The data from trisomy 13 and trisomy 18 pregnancies, (four single umbilical arteries in 15 pregnancies) when compared with trisomy 21 pregnancies (no single umbilical arteries in 18 cases), reaches statistical significance (two-tailed Fisher's exact test, $p = 0.033$). Additionally there was no evidence of a single umbilical artery in 11 cases of sex chromosome abnormalities (including eight cases of monosomy X).

It is noteworthy that there was no apparent association in this series of a single umbilical artery with any other specific morphologic abnormality. It could be theorized that a single umbilical artery is a vascular anomaly and therefore might have an association with congenital heart defects. The pathologic examination of those fetuses with a single umbilical artery included a thorough internal dissection in only three cases, but in two of the three cases the single umbilical artery was noted in the presence of an anatomically normal fetal heart. This suggests that a single umbilical artery is at least not a direct sequela of congenital heart defects.

Single umbilical artery is a congenital malformation that appears to provide information and may help in differentiating between certain cytogenetic abnormalities. Medical professionals may not take note of it at the present time. This is well demonstrated by the inability to document the number of umbilical arteries in our attempts to obtain pathologic and clinical follow-up on these cytogenetically abnormal pregnancies. Observation of the number of umbilical arteries is something that can be done on gross examination and this

noninvasive information can be obtained at little or no cost after delivery of the pregnancy.

Before delivery the number of umbilical vessels may be able to be ascertained by ultrasonographic examination.[9-12] The incidence of aneuploidy when a single umbilical artery is noted prenatally remains unknown. The identification of a single umbilical artery in the presence of a central nervous system malformation is suggestive of aneuploidy (trisomy 13 or trisomy 18).[9] Therefore, when congenital malformations are noted on ultrasonographic examination prenatally, discerning the number of umbilical vessels may be possible and may be useful in suggesting specific cytogenetic diagnoses. For example, in the case of a congenital heart defect or in the case of a cystic hygroma, finding two umbilical vessels would appear to lead one away from trisomy 21 or monosomy X as a cytogenetic diagnosis and toward trisomy 13 or trisomy 18 as possible diagnoses.

The presence of a single umbilical artery is associated with anatomic and karyotypic abnormalities. It is information that is easily obtained at delivery and may be noted prenatally on sonographic examination. The documentation of this information in the clinical record would therefore seem warranted.

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Transcervical chorionic villus sampling and amniocentesis: A comparison of reliability, culture findings, and fetal outcome

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We evaluated the reliability, culture findings, and fetal outcome after transcervical chorionic villus sampling or amniocentesis in a group of 860 patients. All procedures were performed for the indication of advanced maternal age with consistent procedure and laboratory techniques. Successful procedures were completed in 97.7% (420/430) of patients in the chorionic villus sampling group, compared with 99.5% (428/430) in the amniocentesis group ($p < 0.01$). Success was more frequent with only one attempt in the amniocentesis group (427/428) versus 354 of 420 in the chorionic villus sampling group ($p < 0.001$). Culture failure was more common after chorionic villus sampling ($p < 0.001$). Pregnancy loss rates through 28 weeks' gestation and the entire gestation were not significantly different. The prevalence of preterm delivery did not vary between groups, but birth weights of infants in the chorionic villus sampling group were significantly greater. In summary, the present investigation supports previous findings that chorionic villus sampling is a safe alternative to amniocentesis and is not associated with long-term pregnancy complications. (Am J Obstet Gynecol 1990;163:926-31.)

Key words: Transcervical chorionic villus sampling, amniocentesis, prenatal diagnosis

Transcervical chorionic villus sampling (CVS) is a relatively new addition to the armamentarium of prenatal diagnostic techniques; consequently questions remain concerning its reliability and safety.[1-3] Recently, multiinstitutional collaborative trials have attempted to address these issues by comparing CVS with amniocentesis, but such studies suffer from differing indications for the procedures and from variability of operator experience, operative technique, and type of catheter or gauge of needle used, both within and between institutions.[4, 5] In an attempt to overcome these potentially confounding variables, we compared the outcome of pregnancies in which chorionic villus sampling or amniocentesis was performed by only two persons at a single institution with consistent procedure and laboratory techniques for the sole indication of advanced maternal age. In addition, the efficacy and accuracy of each procedure was ascertained.

Material and methods

In the Prenatal Diagnosis and Treatment Center in the Department of Obstetrics and Gynecology at the University of Virginia Health Sciences Center, transcervical CVS was performed on 669 patients between December 1986 and June 1989. Our study group comprised all patients with singleton gestations with advanced maternal age as the sole indication and whose estimated date of confinement was before July 18, 1989 ($n = 430$). The CVS program was initiated in November 1985 after approval was obtained from the Human Investigation Committee. More than 140 procedures and cytogenetic analyses were performed before the initiation of this study. Patients in whom an amniocentesis was attempted were selected for comparison with the patients undergoing CVS by review of the Center's log book of procedures and identification of the most recent 430 consecutive patients whose estimated date of confinement was on or before July 15, 1989. These patients also had singleton gestations, and their procedures were performed for the indication of advanced maternal age. Physicians and laboratory personnel were likewise experienced in the performance of amniocentesis and cytogenetic analysis inasmuch as approximately 800 procedures had been completed during the year preceding the initiation of this study. The majority of the patients who were seen in the Center were referred from outside the institution and the patient and her physician, before referral and evaluation by us, had jointly decided whether CVS or amniocentesis was desired. After the diagnostic procedure was completed, management of pregnancy was at the discretion of the patient's physician.

All procedures were performed by either of two operators (W. A. H. or J. E. F.). For all patients, information concerning the pregnancy and procedure was

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prospectively coded on the data forms at the time of the patient visit. Gestational age was determined by a combination of the last menstrual period and standard ultrasonographic biometric parameters.[6] If the gestational age as determined by ultrasonography was discrepant by more than 1 or 2 weeks, respectively, in patients in the first or second trimester of pregnancy, then the gestational age derived by ultrasonography was used. In all instances, fractions of a week were converted to the appropriate decimal equivalent for coding.

CVS was performed on patients between 9 and 12 weeks' gestational age, as previously described.[1, 7] All samples were obtained with 16-gauge polyethylene catheters (Angiomed, West Germany). In no instance were greater than three attempts made. A new catheter was used for each attempt. The samples were immediately inspected by the operator under a dissecting microscope to determine that a sufficient amount (>10 mg) of villi had been obtained. Villi were dissected free of all maternal tissue and placed into culture.[1] "Direct" preparations of villi were performed by the method of Gibas et al.[8] but were used only for confirmation of long-term culture results.

Amniocenteses were performed under direct ultrasonographic visualization with a 22-gauge needle. The amniotic fluid cells were then cultured in standard fashion with both a cover-slip and flask method.

An attempted CVS was defined as passage of the catheter through the endocervical canal into the chorion frondosum and suction applied. An amniocentesis attempt was defined as the needle being placed through the maternal abdomen and into the uterus. For both procedures, "success" was defined as occurring if a sufficient amount of the appropriate material for culture was obtained; a "failed" procedure occurred when an attempt was made but these criteria were not met. Pregnancy follow-up information was routinely solicited for all patients by writing to their physicians. Requested data included birth weight, gestational age at delivery, infant gender, pregnancy complications, infant malformations, if present. If these questionnaires were not returned, follow-up letters were sent or phone calls were placed to physicians and patients to obtain pregnancy outcome information. A pregnancy was considered to have been terminated for patient desire if termination occurred at the patient's request without any chromosomal or other fetal abnormality. Preterm delivery was defined as delivery before 37 weeks' gestation (259 days).

Culture failure occurred when, despite obtaining a sufficient amount of the appropriate material for culture, cytogenetic analysis could not be completed. A cytogenetic abnormality was stated to exist when a deviation from normal chromosome number or morphology was identified.

Patient and procedure information was maintained on an Apple Works data base system. Statistical analysis of the data used either a Student t test, χ^2 tests (2×2 or 3×2) with Yates' continuity correction factor, or the Fisher exact test when applicable.

Results

The patient characteristics for the 860 women who met the above parameters for inclusion and had CVS or amniocentesis performed are depicted in Table I. It can be noted that the patient groups were comparable with respect to the number of live-born children, history of prior spontaneous and elective abortions, the percentage whose race was white, and the percentage who received prenatal care before the procedure. The maternal age at the time of the procedure was somewhat greater in the patients in the CVS group.

Chorionic villus sampling procedures were performed at a mean gestational age of 10.3 ± 0.7 weeks (range, 8.8 to 12.2 weeks). Amniocentesis was performed at a mean gestational age of 16.9 ± 1.4 weeks (range, 12.7 to 23.7 weeks). "Early amniocentesis" was not routinely offered during the interval encompassed in this study and only two procedures were attempted at gestational ages earlier than 14 weeks. There were 10 failed procedures in the women in the CVS group compared with two failed procedures in women in the amniocentesis group ($p < 0.05$). The two failed procedures in the amniocentesis group occurred after attempted amniocentesis at 18 and 21 weeks' gestational age, when the laboratory determined that maternal urine had been withdrawn rather than amniotic fluid. Each patient was obese and had a repeat amniocentesis without incident. The 10 failed CVS procedures occured when either no tissue or only decidua was obtained. In these 10 patients in whom CVS failed, the procedure was discontinued when it was decided tissue could not be obtained after two attempts in six cases and after only one attempt in the remaining four; in no instance were three attempts made in this group. The failed CVS procedures were distributed randomly over the interval of this study. These procedures were believed to have failed because of an inaccessable placental location in six cases, a combination of leiomyomata uteri and placental location in two cases, and difficulty caused by leiomyomata or a severely retroverted uterus in one instance each. Of these 10 patients, failed CVS procedures occurred in three before the introduction of transabdominal CVS into our program. The gestational age and reason for failure in each precluded rescheduling a later transcervical CVS attempt and they were offered and accepted midtrimester amniocentesis. In three of the remaining seven patients, placental location enabled us to offer and successfully perform transabdominal CVS. In the remaining four

Table I. Characteristics of patients undergoing CVS or amniocentesis

Characteristic	*CVS*	*Amniocentesis*	*p Value*
Maternal age (yr)*	36.8 ± 2.2	36.5 ± 2.2	<0.05
No. live-born children (%)			
0	22.9	26.9	NS
1	40.2	39.2	NS
2	26.6	23.5	NS
≥3	10.3	10.4	NS
No. of prior miscarriages (%)			
0	63.8	65.9	NS
1-2	33.6	31.7	NS
≥3	2.6	2.4	NS
History of elective abortions (%)	22.4	20.8	NS
White race (%)	96.5	95.2	NS
Prenatal care before procedure (%)	98.8	99.5	NS

*Mean ± SD.

Table II. Number of attempts required in the patients in whom CVS or amniocentesis was successful*

	Single attempt	*Two attempts*	*Three attempts*
CVS	354	61	5
Amniocentesis	427	1	0

*$p < 0.001$.

patients, transabdominal CVS was not offered because it was judged that the placental location would have precluded success. In two of these four patients, limitations because of gestational age did not allow a repeat attempt at a later date and they, too, were offered and accepted midtrimester amniocentesis. In the other two patients, it was believed that interval growth would allow successful repeat CVS procedures 1 week later; such was the case in each.

As can be noted in Table II of the successful amniocentesis procedures, one attempt was required to obtain sufficient material for culture in all but one patient. In the successful CVS group 61 patients (14.5%) required two attempts and five (1.2%) required three attempts. This difference was significant ($p < 0.001$).

There were no failed cultures in the 428 women in whom amniocentesis was successful as compared with 12 instances in the patients who had successful CVS procedures ($p < 0.01$). Patients in the CVS group who had failed cultures had an average of 25 mg of villi obtained (range 10 to 40 mg). In the 12 cases of failed CVS cultures, "direct" preparations of villi failed in five and were not set up in two cases. In five instances, the direct preparation revealed a normal chromosome complement and was available for reporting, but it was the policy of our Center to not report results just on the basis of the direct preparation. In addition, the occurrence of culture failure was evaluated in relationship to laboratory experience over the duration of the study. Culture failures were evenly distributed over time, and there was no indication that laboratory success improved as the study continued. Thirteen cytogenetic abnormalities (3.2%) were detected in the 408 CVS patients in whom culture was successful as compared with nine abnormalities (2.1%) in the 428 patients in the successful culture amniocentesis group (p = NS). Cytogenetic abnormalities in the CVS group included trisomy 21 ($n = 7$), trisomy 18 ($n = 3$), mosaicism ($n = 2$), and marker chromosome ($n = 1$). The mosaicism seen in the CVS culture included tetraploidy (26% of cells) and trisomy 13 (10% of cells). Seven cases of trisomy 21 and one case each of pseudomosaicism (trisomy 18 in one cell) and an unbalanced translocation were encountered in patients in the amniocentesis group. Patients in the CVS and amniocentesis group with mosaicism were further evaluated with amniocentesis or fetal blood sampling, respectively, and had normal chromosome results. Therefore these pregnancies were continued and these infants were chromosomally and phenotypically normal.

To evaluate outcome in the pregnancies that were "intended to continue," the cases that were terminated for diagnosis or request were removed from the total number of procedure attempts in each group. In the CVS group, there were 13 pregnancy terminations (11 cytogenetic abnormalities, 1 anencephaly, and 1 for apparent sex selection that was unknown to us at the time of procedure), resulting in 417 continuing pregnancies. Eight pregnancies (all cytogenetically abnormal) were terminated in the amniocentesis group, leaving 422 "intended to continue." In Table III pregnancy outcome is tabulated. Differences in pregnancy loss at gestational ages ≤28 weeks and total pregnancy loss rates were not significantly different. Of the four pregnancy losses in the amniocentesis group before 28 weeks' gestation, two were fetal deaths with associated bleeding and cramping at 20½ weeks; one was a spontaneous abortion at 19½ weeks; and one was stillborn at 26 weeks' gestation. The remaining two pregnancy losses

Table III. Pregnancy outcome

	CVS		Amniocentesis		
	No.	%	*No.*	%	*p Value*
Procedures attempted	430	—	430	—	—
Intended to continue	417	—	422	—	—
Pregnancy loss					
<28 weeks	10	2.4	4	0.9	NS
All weeks	11	2.6	6	1.4	NS
Live birth	406	—	416	—	—
Term	385	94.8	389	93.5	NS
<37 wk	21	5.2	27	6.5	NS
Birth weight (gm)	3499 ± 597	—	3408 ± 654	—	<0.05

in the amniocentesis group were stillborn fetuses at 29 and 40 weeks' gestational age. In none of these losses was more than one attempt at amniocentesis required. There were 10 pregnancy losses before 28 weeks' gestation in the CVS group; all occurred before 20 weeks' gestation (range, 7 days to 10 weeks after the procedure). In the 10 pregnancy losses at <28 weeks' gestation in the CVS group, seven occurred within 3 weeks of the procedure and were associated with bleeding and cramping. Two additional patients had similar symptoms and pregnancy loss at 4 and 8 weeks after the procedures. The final patient was noted to have persistent spotting after the procedure and ultrasonography at 18 weeks' gestation documented oligohydramnios; spontaneous abortion occurred 2 weeks later. In four of the 10 patients, two attempts were required, in none was three required. The solitary loss beyond 28 weeks' gestation in the CVS group was a 34-week stillborn fetus in which a single attempt was required.

The mean maternal age, gestational age at the time of the procedure, and amount of chorionic villi sampled were not significantly different when patients with fetal losses were compared with those with no losses. In addition, there was no significant relationship between the number of CVS attempts and the risk of fetal loss.

There was no difference between procedures in the incidence of preterm deliveries. However, the mean birth weight was greater in the infants in the CVS group (3499 ± 597 gm) when compared with infants in the amniocentesis group (3408 ± 654 gm) ($p < 0.05$). There was no serious maternal morbidity in either group.

Comment

Since its introduction in the early 1970s amniocentesis, coupled with cytogenetic analysis of cells in the amniotic fluid, has been considered the standard test for prenatal diagnosis. However, the belief that amniocentesis should be considered the standard test has been questioned recently as generally reassuring information has accumulated about CVS.[9] CVS is gaining wide acceptance by patients and physicians alike because it offers the possibility for early results. However, complete information about its safety, efficacy, and accuracy is essential before CVS can be implemented on a large scale. To address these issues, several collaborative trials have been performed. The drawback of these trials was that variability existed in operator experience, as well as the procedure and laboratory techniques used.[4,5] For instance (although it is understandable because CVS was a relatively new technique at the time), in the U.S. Collaborative trial, each operator had to have completed only 10 CVS procedures and each center only 25 to begin the study.[4] In the Canadian trial, criteria for "reasonable experience" by the operator and cytogenetics laboratory were somewhat more stringent, but the CVS techniques varied from center to center, as did the cytogenetics techniques, gauge of amniocentesis needle, and use of ultrasonography during amniocentesis.[5] The experience of amniocentesis operators was not addressed in either study, and thus it is possible that amniocentesis procedures were relegated to relatively inexperienced personnel. All these factors could have unwittingly biased the comparison between CVS and amniocentesis. Our study attempted to overcome some of these potential deficiencies by selecting patients at a single center in whom the procedures were performed only for the indication of advanced maternal age by two operators who were experienced and used consistent CVS and amniocentesis techniques. Laboratory methods were well established and consistent, as well.

Our results indicate that each procedure is highly successful at obtaining the appropriate material for culture. Although amniocentesis is more likely to be successful both overall and with one attempt only, the incidence of failed CVS procedures (10/430 or 2.3%) is quite acceptable, and similar to that reported in other series.[1,10] In addition, of the patients in whom CVS failed, in all it was possible to obtain a cytogenetic di-

agnosis by offering them transabdominal CVS, amniocentesis at a later date, or by repeating the transcervical CVS procedures in 1 week. We believe these differences between the CVS and amniocentesis groups underscore the fact that CVS is inherently a somewhat more difficult procedure to perform.

Culture failure was, likewise, more common in the CVS patients compared with patients in the amniocentesis group. In most instances there was no explanation for the failed cultures, despite adequate sample size. We do not believe laboratory inexperience was responsible for the failures because at least 140 CVS cultures had been set up and evaluated before processing the villi from patients in this study. The U.S. Collaborative study and Canadian trial, likewise, noted a greater likelihood of culture failure in CVS patients.[4, 5] On the contrary, Wright et al.[11] showed tissue culture failure to be less common in CVS.

Similar to other studies[4, 11] the incidence of cytogenetic abnormalities was not significantly different when compared between groups. There were no errors in diagnosis in either group. The incidence of mosaicism was comparable in both CVS and amniocentesis. Further evaluation in all cases documented a normal fetal chromosome result and all pregnancies continued with normal outcomes.

Our data indicate that pregnancy loss rates before 28 weeks' gestation and through the entire gestation were not significantly different between the CVS group and patients in the amniocentesis group. This result is in close agreement with the U.S. Collaborative Trial.[4] Whereas this is reassuring information for us to provide to patients seen in our Center, this reassurance must be tempered somewhat because our study was not randomized and we did not evaluate all socioeconomic factors that could have possibly affected pregnancy outcome, such as level of income or education. Also, despite the fact the study encompassed 2 ½ years and 860 subjects, the power of such a conclusion is rather low (36%). It is important to remember, however, that an "uncorrected" comparison of pregnancy outcome such as we report does not take into account the well-known fact that there is a background rate of loss between the 9 to 12-week interval of pregnancy and the 16 to 18-week interval. Because we did not see patients undergoing amniocentesis before referral, they could not be evaluated during weeks 9 to 12 of pregnancy to establish the pregnancy loss rate between that interval of gestation and when amniocentesis was undertaken. However, by combining the data in this study with that from the U.S. Collaborative Study, we can more realistically estimate the risk of CVS compared with amniocentesis. From the latter study information on the approximate pregnancy loss rate between 9 and 16 weeks' gestation is available; after a normal ultrasonographic examination at 9 to 12 postmenstrual weeks, 2.5% of the pregnancies were lost before a 16-week evaluation.[4] With the methods outlined by Rhodes et al.,[4] the total (overall) rate of loss of desired pregnancies (spontaneous losses plus pregnancy terminations) in our study was 5.8% in amniocentesis patients and 5.6% in CVS patients. Thus when this method is used to evaluate outcome our data further support the previous studies that there is no statistically significant difference in risk between CVS and amniocentesis.[4, 5] Use of this "corrected" data allows for a more valid comparison between techniques and increases both the statistical power (>80%) and our confidence in our findings that there is no difference in loss after CVS or amniocentesis.[12] Although there are inherent limitations when data from other patient populations are used, the essentially identical loss rates in this study strongly suggest that CVS does not have an increased risk of fetal loss if performed by experienced personnel.

The incidence of preterm delivery in the CVS and amniocentesis groups was not different and supports the results reported in both collaborative trials.[4, 5] We noted a slight, but significant, increase in birth weight of infants in the CVS group compared with those in the amniocentesis group. This outcome may reflect subtle differences in socioeconomic factors that were not included in the demographic data obtained on each patient. Our study suggests that long-term complications from CVS are not increased over those encountered when amniocentesis is used.

In summary, the present investigation supports previous suggestions that CVS is a safe procedure. There is no significant increase in fetal loss or long-term pregnancy complications over that seen with amniocentesis. Alternatively, our results indicate that despite extensive operator and laboratory experience, obtaining and successfully culturing a sample is significantly more likely with amniocentesis. Of patients in the CVS group, 24 required a subsequent diagnostic procedure (patients with mosaicism, procedure or culture failures), whereas only three patients in the amniocentesis group had further studies (patients with procedure failures or mosaicism). Patients seeking prenatal diagnosis should be informed of these differences, especially in beginning programs in which the prevalence may be much higher. However, the relative safety of CVS and earlier gestational age at which it can be performed may outweigh this disadvantage. Overall, we believe CVS offers a safe and reliable alternative to amniocentesis.

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Second-trimester placental biopsy for rapid fetal karyotyping

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Since January 1988 the technique of first-trimester chorionic villus sampling (placental biopsy) has been extended to include cases in the second trimester. To date, 40 procedures have been performed. The main indication for the late chorionic villus sampling was a low serum α-fetoprotein value in association with an increased risk for Down syndrome (n = 28), abnormal ultrasonographic finding (n = 7), and failed amniotic cell culture (n = 3). Successful karyotype results were achieved in all but two cases. Most results were obtained within 48 hours with direct cytogenetic techniques. No cases of mosaicism were found. The highest yield of abnormal karyotypes was obtained from the cases with abnormal ultrasonographic findings (one trisomy 21, two 45,X). One case of trisomy 21 was identified in the 28 cases of low serum α-fetoprotein. No spontaneous losses have occurred. The technique is easy to learn, does not differ from first-trimester procedures, and may have a lower complication rate than cordocentesis.The reporting of cases to the *CVS Newsletter* should help evaluate late chorionic villus sampling as another method for rapid fetal karyotyping. (AM J OBSTET GYNECOL 1990;163:931-4.)

Key words: Placental biopsy, rapid fetal karyotyping, chorionic villi

Amniocentesis performed in the second trimester of pregnancy is still the "gold standard" test for the detection of fetal karyotype abnormalities. The disadvantage of this technique is that results are not available for 2 or 3 weeks. This is particularly unacceptable in late pregnancy, when knowledge of the fetal karyotype is essential for obstetric management when certain structural defects are present in the fetus.

Chorionic villus sampling or placental biopsy, unlike amniocentesis, does not require culture for immediate karyotype analysis. The direct method as described by Simoni et al.[1] yields results within 48 hours. The technique has been shown to be feasible when performed

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Table I. Midtrimester placental biopsy ($N = 40$)

Factor	*Average*	*Range*
Patient age (yr)	32.4 ± 5.0	19-42
Gestational age (wk)	18.6 ± 2.1	15-26
Weight of sample (mg)	11.1 ± 5.9	1-2

Table II. Karyotype abnormalities detected by midtrimester placental biopsy

Indication for biopsy	*Karyotype*
Oligohydramnios	47,XY + 21
Cystic hygroma	45,X
Low maternal serum α-fetoprotein	47,XY + 21
Fetal hydrops	47,XY + 21
Cystic hygroma	45,X

after the first trimester.[2-6] This study presents the clinical and laboratory results of an initial experience with placental biopsy in the second trimester of pregnancy.

Patients and methods

The technique of first-trimester chorionic villus sampling is already well established in our center. The procedure used for the second-trimester placental biopsies was identical to the method used for chorionic villus sampling in the first-trimester procedures.

The recruited patients provided informed consent before the procedure. The maternal abdomen and ultrasound transducer were cleaned with a topical application of chlorhexidine gluconate (0.5%). No local anesthetic was given. Ultrasonographic scanning was performed to determine the placental location. Patients with a deep posterior placenta were excluded from the study because placental biopsy would have required a transamniotic approach with possible increased fetal hazard. Sampling was done under real-time ultrasonographic guidance with a curvilinear probe (Diagnostic Sonar 128, 3.5 MHz, Diagnostic Sonar, Livingston, Scotland). A 16-gauge intravenous cannula with a stylet was introduced through the maternal abdominal wall until it just penetrated the uterine wall directly above the chosen sampling site. The stylet was removed and a 20-gauge 90 mm spinal needle with a stylet was then introduced. When the echo of the needle tip was clearly visible within the placenta, the stylet was removed and was replaced by a 10 ml syringe. The needle was then moved back and forth within the substance of the placenta close to the chorionic plate with 10 ml of constant suction. This action was continued for approximately 10 to 15 seconds and the needle was then withdrawn.

Aspirated tissue was washed in a 10 cm plastic Petri dish with Ham's F-10 solution and was examined by eye to estimate tissue weight. When a suitable quantity of tissue was seen, the sample was taken to the laboratory for processing. At the end of the procedure the fetus and the placenta were carefully examined and any abnormal findings were noted.

In the laboratory the villi were washed in fresh media, cleaned, and sorted to remove blood clots and carefully inspected under an inverted microscope to remove any maternal decidua. An estimate of villus weight was made according to reference standards; then 2 to 3 mg of tissue was removed for long-term cultures. The remaining villi were transferred to RPMI medium and incubated at 37° C for 1 hour before adding colcemid (0.1 μg/ml final concentration) for 2 hours. The villi were then harvested according to the method of Simoni et al.[1] for direct preparations. Cell cultures from villi were established in Chang medium and suspension harvests were prepared according to standard techniques. Direct preparations were analyzed on 10 cells stained with giemsa. In all cases G banding was attempted. Cultured preparations were analyzed from at least two cultures of G-banded cells.

Results

The technique of second-trimester placental biopsy was introduced in January 1988. In the first year of the study 12 procedures were done and an additional 28 biopies were performed in 1989. The overall results are shown in Table I. The high mean patient age reflects the number of patients who had the procedure performed because of an increased risk of aneuploidy because of low maternal serum α-fetoprotein estimation ($n = 28$). Two cases were performed because of previous karyotype abnormalities, and three procedures were performed because of failed amniotic fluid culture. Seven procedures were done when an abnormal ultrasonographic appearance suggestive of chromosomal abnormality was detected. Suitable samples of villi were obtained in 38 of the 40 cases. The mean weight of chorionic villi aspirated was 11.1 mg. This was achieved with either one or two attempts at aspiration. Four cases had only direct chromosome preparations performed. In five cases culture results only were achieved, and in 27 cases both direct and culture results were obtained. In two cases no result was obtained from placental biopsy. The average time for karyotype results to be obtained using culture techniques was 20 days (range, 16 to 30 days) and the mean time for direct results was 2 to 3 days (range, 1 to 6 days).

The highest yield of karyotype abnormalities was found in the cases with abnormal ultrasonographic findings (two cases of trisomy 21, two of 45,X). One other case of trisomy 21 was identified in the 25 cases of increased risk for Down syndrome (Table II). All

women whose fetuses had abnormal karyotypes elected to have termination of pregnancy. Except these pregnancy terminations, no cases of fetal loss have been reported. To date, 20 patients have been delivered with no neonatal complications reported. The other pregnancies are continuing.

Except for one case in which only tetraploid cells were seen on direct preparations and a 46,XX karyotype subsequently was obtained from cultures, there were no cases of discordant karyotypic findings or problems as a result of mosaicism on direct preparations or cultures in this series.

Comment

This study shows that the technique of chorionic villus sampling used in first-trimester cases can equally be applied in later pregnancies. The technique is easy to learn and has the advantage that preliminary karyotype results can be obtained within 2 to 3 days. This shortened interval helps to relieve patient anxiety and may influence obstetric decision making.

Patient selection methods for second-trimester placental biopsy are arbitrary, but in this study selection was limited to patients with an increased risk of having a fetus with an autosomal trisomy or to patients with a demonstrable fetal abnormality on ultrasonography and a significant chance of a karyotype abnormality. Screening for increased risk of autosomal trisomy is performed on all patients attending our center who wish maternal serum α-fetoprotein testing for the detection of neural tube defects. The risk of autosomal trisomy is calculated with figures previously reported.[7] An arbitrary cutoff level of 1:200 for Down syndrome was taken as the level at which patients are counseled concerning the risk of Down syndrome. Prenatal diagnosis by either amniocentesis or midtrimster placental biopsy is then offered to all patients with a risk $\geq 1:200$.

The decision to perform either amniocentesis or placental biopsy also depends on the placental site. In this study, unlike previous reports,[5] only anterior or posterofundal placentas were sampled by the technique described. No biopsies were attempted when amniotic sac puncture would have been required to obtain a sample. Placental location did not appear to influence the frequency of needle insertions. The results show that an adequate sample can be obtained in the majority of cases with a maximum of two needle insertions. Four cases had failed results; two of these were a result of inadequate sample size and the other two remain unexplained. Over the period of the study sample sizes have improved; the mean sample size for the last 28 cases was 15 mg. A sample size >10 mg was usually adequate for both direct and culture cytogenetic methods, but successful results were obtained in some samples as small as 5 mg. No relationship was apparent between the sample size and the time required to report both direct and culture results.

It appears that results of this study agree with the findings of previously reported studies on midtrimester placental biopsy in that the mitotic index does not fall with placental aging,[2-6] at least until 26 weeks' gestation, which was the latest gestation at which the procedure was performed. In the study by Nicolaides et al.,[2] successful karyotypes were obtained in two cases sampled in the third trimester (35 and 37 weeks). In a study by Wolstenholme et al.,[6] the mitotic index was variable and the quality of the preparations did not always correspond well with the quality and quantity of the specimen.

The main benefit of placental biopsy is that rapid karyotyping can be made available from direct cytogenetic techniques. It must be stressed that in this study the direct results were regarded as preliminary, and although the patient was told of these results, she was also told that a culture result would require another two weeks. However, it was thought that the direct results were sufficiently accurate to exclude a major karyotype abnormality such as trisomy 21. It should also be emphasized that in a relatively large number of cases (5/38, 13%) no direct results were achieved. This is in contrast to our laboratory's experience of first-trimester chorionic villus sampling in which inability to obtain direct results occurred in 4.6% of cases. A recent large study[8] reported a false-postive rate in direct preparations of first-trimester chorionic villus samples of 2.3%. This primarily comprised mosaicism confined to the trophoblast. Such a study stresses the need for confirmatory culture results. However, should culture results not be available because of a poor sample size, it is reassuring that no false-negative results were obtained in the direct cytogenetic preparations. In our laboratory's experience of first-trimester chorionic villus samples, 1% of direct preparations had a mosaic karyotype. However, on follow-up a false-positive rate of 0.75% was seen. No cases of mosaicism have been found in any of the second-trimester placental biopsies.

Of the abnormal karyotype results obtained, all were reported from direct preparations. Thus a result was available within 48 hours and this aided in the management of the case.

To date, except the patients who chose pregnancy termination, no cases of fetal loss have occurred after the procedure. These preliminary results are considered encouraging and are similar to the experience of 20 other centers worldwide that have now been incorporated into a late chorionic villus sampling registry.[9] The sampling technique is easy to learn, does not differ from first-trimester procedures, and may have a lower complication rate than cordocentesis.[10] The procedure is useful for patients who are seen too late for first-trimester prenatal diagnosis, for those who are esti-

mated to have a high risk of having a fetus with autosomal trisomy, and for those patients in whom an amniotic fluid cell culture fails. It may prove to be of particular value in cases of abnormal fetal anatomy as demonstrated ultrasonographically. Exclusion of a chromosome abnormality in such cases enables appropriate management of the anomaly in terms of in utero therapy or the mode of delivery. The reporting of cases to the *CVS Newsletter* in Philadelphia should help evaluate placental biopsy as another method for rapid fetal karyotyping.

We thank the members of the scientific staff in the Duncan Guthrie Institute of Medical Genetics, Glasgow.

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The association of maternal floor infarction of the placenta with adverse perinatal outcome

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Maternal floor infarction of the placenta is a relatively rare disorder that on gross examination is characterized by a thickened gray-yellow maternal floor of the placenta with histologic evidence of massive fibrin deposition involving the decidua basalis and the contiguous villi. This lesion has been associated with fetal death, preterm delivery, and intrauterine growth retardation and is thought to be recurrent. Sixty cases of maternal floor infarction were identified in 48 women. Fetal death occurred in 24 of the 60 cases (40%). Preterm birth occurred in 21 of 36 (58.3%) live-born infants, and 19 of the 35 (54.2%) live-born infants for whom a birth weight was known had evidence of intrauterine growth retardation. Among the 41 multiparous patients in our series there were five documented recurrences (12.2%). Review of the past reproductive history of these 48 patients (196 pregnancies) demonstrated a significant incidence of fetal death (24.1%), intrauterine growth retardation (31.3%), and preterm death (35.4%). The association of fetal death and maternal floor infarction emphasizes the importance of a placental examination with all cases of fetal death and infants with intrauterine growth retardation. Given the risk of recurrence, the identification of maternal floor infarction should alert the clinician to the potential for growth retardation, preterm birth, and fetal death in subsequent pregnancies. (Am J Obstet Gynecol 1990;163:935-8.)

Key words: Placenta, intrauterine growth retardation, fetal death

Benirschke and Driscoll first described maternal floor infarction of the placenta.[1] The findings on gross examination include a thickened, yellow maternal floor with large deposits of fibrin. (Fig. 1). Microscopically, the villi are often encased in the fibrin and eventually become necrotic and avascular (Fig. 2). Maternal floor infarction is to be distinguised from the more common focal placental infarcts in that ischemic tissue necrosis is typically absent. The pathologic changes seen with preeclampsia (i.e., decidual vasculopathy) are absent in cases of maternal floor infarction and there is no evidence of acute or chronic villitis.

This entity has been reported to be associated with recurrent fetal death and intrauterine growth retardation[2-4] and yet it has not been explored in depth. The purpose of this investigation was to determine the incidence of maternal floor infarction of the placenta, to clarify its association with fetal death, IUGR, and preterm delivery, and to study the rate of recurrence in subsequent pregnancies.

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Material and methods

The medical records of all patients with the diagnosis of maternal floor infarction of the placenta made at the University of California, San Diego, Medical Center from Jan. 1, 1976, through Dec. 31, 1987, were reviewed. The diagnosis of maternal floor infarction was confirmed by one of us (K. B.) and was based on a marked increase in fibrin deposition involving the decidual floor with villous encasement.

Fetal death was defined as a pregnancy loss at >20 weeks' gestation and preterm birth was defined as delivery at <37 weeks' gestation. The designation of IUGR was applied to newborns whose birth weights were less than the 10th percentile for gestational age.[5]

The incidence of fetal death, infants with IUGR, and preterm delivery was then determined for the 60 known cases of maternal floor infarction and for the 196 pregnancies constituting the total reproductive history of these 48 women. Medical records were available for all 60 of the known cases. Twenty-five of the 48 women were interviewed and provided additional information regarding their reproductive histories.

Results

Sixty cases of maternal floor infarction of the placenta were diagnosed in 48 women. Thirty were from inborn babies and the remaining 30 were from placentas sent to our institution for pathologic consul-

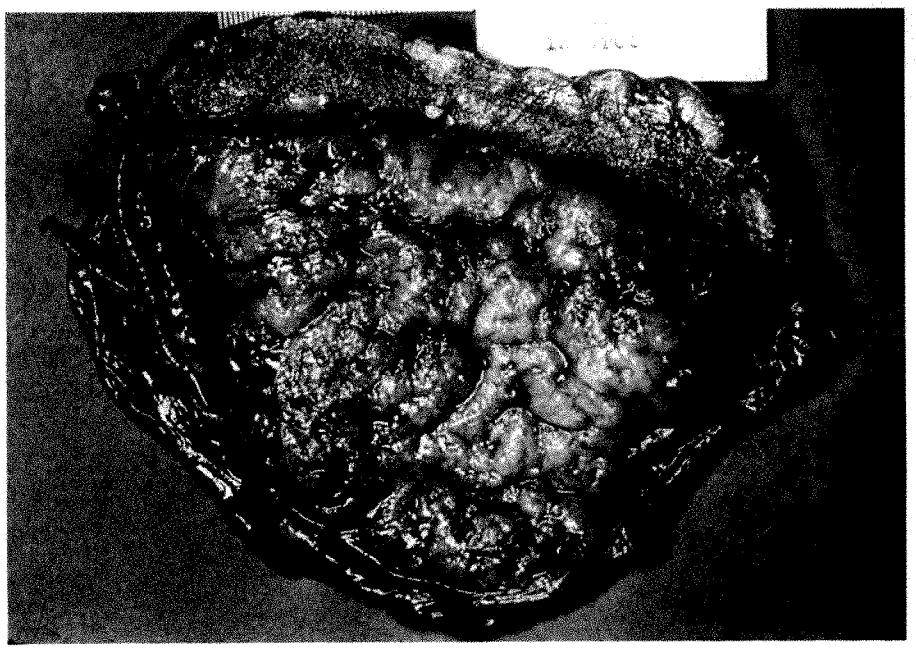


Fig. 1. Characteristic gross appearance of maternal floor infarction with thickened and yellow maternal floor.

Table I. Incidence of fetal death, IUGR, and preterm delivery in patients with maternal floor infarction of the placenta

Outcome	*Incidence*
Fetal death	24/60 (40%)
IUGR	19/35 (54%)
Preterm delivery	21/36 (58%)

tation. The incidence of maternal floor infarction was 30 in 32,182 (0.09%). The reproductive experience of these 48 women (including the 60 known cases of maternal floor infarction) totaled 196 pregnancies with 51 (26%) ending in either a spontaneous or an elective abortion. Thus 145 pregnancies were included in the analysis of the patients' collective reproductive histories.

Twenty-four of the 60 known cases of maternal floor infarction were associated with fetal death (40%) (Table 1). Ten of 24 (42%) occurred between 30 and 34 weeks of gestation. Overall 35 fetal deaths (24.1%) were reported in the 145 pregnancies that extended beyond the 20th week of gestation.

A birth weight less than the 10th percentile was recorded for 19 (54.2%) of 35 live-born infants delivered of patients with known maternal floor infarcts (Table I). Twenty of the 22 (91%) stillborn infants with known birth weights were below the 10th percentile. They were excluded from the analysis, given the difficulty in accurately assigning gestational age to an intrauterine fetal death.

Twenty-one of the 36 (58.3%) live-born infants with a known maternal floor infarction of the placenta were delivered at <37 weeks of gestation (Table I). Eleven patients were diagnosed with preterm labor that was unresponsive to tocolytic therapy, and there were indications for preterm delivery in the remainder. In the 110 live-born infants among the 48 women in our series, 39 (35.4%) were delivered before 37 weeks.

There were 41 multiparous patients, and 5 (12.2%) of these had documented recurrences. Table II outlines the details of these cases and demonstrates that multiple recurrences were documented in each of the five. Among patients with a maternal floor infarction, a placental examination was performed in 33 subsequent pregnancies. Thirteen (39%) showed gross and histologic evidence of recurrent maternal floor infarction of the placenta.

Comment

Our data suggest a lower incidence of maternal floor infarction than the 0.5% quoted by Naeye[3] in his series from the Collaborative Perinatal Study. The incidence of 0.09% in the current series represents >30,000 consecutive placental examinations from this institution alone.

The association of fetal death and maternal floor infarction in 40% of our 60 cases is striking. The fact

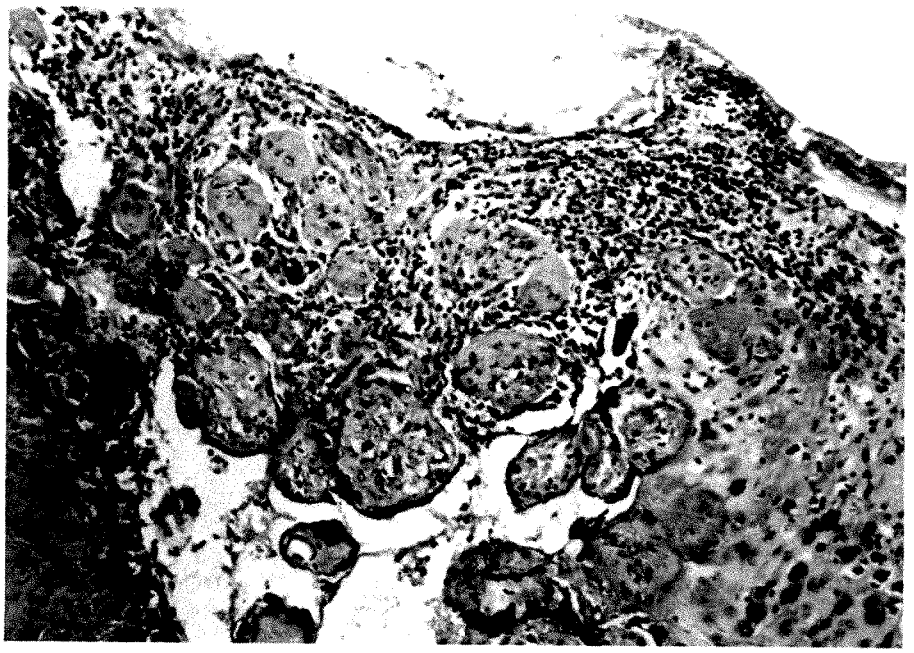


Fig. 2. Massive deposition of fibrin encasing villi with pronounced round cell infiltration.

that our series includes cases referred to one of us (K. B.) for pathologic consultation may introduce an ascertainment bias; however, the 30 cases seen in patients delivered at our institution were also associated with a fetal loss rate of 40%. Naeye[3] found a 17% rate of stillbirth in his series of patients with maternal floor infarction.

The finding of intrauterine growth retardation in 51% of our known cases of maternal floor infarction is similar to the findings of Naeye. Frequently the degree of growth delay is profound and is evident on ultrasonographic evaluation as early as the middle of the second trimester. Nickel[4] described a case of a 690 gm infant delivered at 36 weeks, without other risk factors for IUGR, whose placenta demonstrated the characteristic findings of maternal floor infarction.

The pathophysiologic basis of the fetal death and growth retardation is unclear. It has been suggested that the fibrin deposition interferes with perfusion of the intervillous space and that growth delay and fetal death result from chronic "placental insufficiency."

It has been suggested that maternal floor infarction is a recurrent lesion. Case reports have described recurrent fetal death and growth retardation in women with maternal floor infarction.[1-3] In addition, Naeye[3] found that multiparous women with evidence of a maternal floor infarction had twice as many unsuccessful previous pregnancies (stillbirths and miscarriages) as did multiparous women without maternal floor infarction. In our series we identified five women who had at least one documented recurrence of maternal floor infarction. The actual risk of recurrence is difficult to ascertain because routine placental examination is not performed in cases of growth retardation, fetal death, or preterm delivery. However, among those pregnancies that followed a maternal floor infarction and included placental examination, 39% showed gross and microscopic evidence of recurrent maternal floor infarction.

Table II. Perinatal outcome among patients with recurrent maternal floor infarction of the placenta

Patient No.	*Total pregnancies*	*Maternal floor infarctions*	*Fetal deaths*	*Preterm deliveries*
1	7	4	4	1
2	6	3	2	0
3	7	4	4	2
4	4	4	1	0
5	3	3	3	0

The association of maternal floor infarction with fetal death and intrauterine growth retardation should reinforce the value of a placental examination in such cases. The likelihood that this is a recurrent disorder suggests that once a maternal floor infarction is discovered, subsequent pregnancies are at risk for IUGR, fetal death, and preterm delivery. It would seem prudent to monitor these pregnancies for evidence of fetal growth delay and to perform careful antepartum surveillance to

detect fetal compromise. Delivery should be considered when fetal pulmonary maturity has been established.

This relatively rare but serious placental disorder should be included in the differential diagnosis of fetal death and idiopathic IUGR. Appropriate antepartum management of pregnancy in these patients is likely to improve their chances for a subsequent favorable outcome.

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Placental transfer of cefazolin and piperacillin in pregnancies remote from term complicated by Rh isoimmunization

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Although the administration of prophylactic antibodies for intrauterine transfusion is controversial, little information is available regarding placental transfer of antibiotics administered to the mother, or whether the presence of hydrops affects this placental transfer. Sixteen intravascular intrauterine transfusions were performed in 10 patients. Seven (10 procedures) patients were given 2 gm of cefazolin before the procedure and samples were obtained by fetal vascular access. Three patients (six procedures) were given 4 gm of piperacillin and samples were similarly obtained. Specimens were obtained for fetal serum, maternal serum, and amniotic fluid antibiotic concentration. The mean serum cefazolin concentration in hydropic fetuses was 18.04 ± 3.37 μg/ml, and in nonhydropic fetuses the concentration was 21.02 ± 17.8 μg/ml ($p = 0.72$). The mean fetal serum concentration of piperacillin was 22 ± 12 μg/ml. The placental transfer of both drugs was similar. We conclude that the transplacental passage of these antibiotics is prompt and that the presence of hydrops does not significantly impair the passage of cefazolin. (AM J OBSTET GYNECOL 1990;163:938-43.)

Key words: Placental transfer of antibiotics, hydrops, Rh isoimmunization

Intravascular intrauterine transfusion is a technique that is gaining wide acceptance for management of fetuses with severe blood group isoimmunization. Many modifications of the basic technique have been described, and some authors suggest use of antibiotic prophylaxis to prevent intraamniotic or fetal infection.[1] There are few data available to evaluate the potential fetal benefit of antibiotic prophyalxis, which may be of particular importance in cases of hydrops in which there may be impaired passage of an antibiotic agent across an edematous placenta. The purpose of this study was to determine to what extent maternally administered antibiotics were transferred to the fetus and whether fetal hydrops had an impact on this phenomenon. Cefazolin is a relatively inexpensive first-generation cephalosporin and is frequently used for prophyalxis for both obstetric and gynecologic procedures. Piperacillin is an extended-spectrum penicil-

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Table I. Summary of cefazolin levels in 10 intrauterine transfusions

Patient no.	*Procedure*	*Gestational age (wk)*	*Maternal weight (lb)*	*Hydrops present*	*Time to sample (min)*	*Maternal serum (μg/ml)*	*Fetal serum (μg/ml)*	*Amniotic fluid (μg/ml)*
1	1	23	149	+	40	118	16.6	0.9
	2	25	149	−	40	93	23.4	0.9
2	1	24	138	−	18	80	2.5	0.7
3	1	26	124	+	22	149	23.8	1.1
4	1	30	162	+	22	152	18.2	0.6
	2	32	168	−	43	91	49.2	1.1
5	1	28	208	−	40	93	20.2	1.8
	2	30	206	+	55	62	16.1	0.8
6	1	32	143	−	6	141	9.8	0.6
7	1	24	150	+	8	234	15.5	0.3
Mean + SD						121 ± 50	20 ± 12	0.9 ± 0.4

lin agent with activity against a variety of anaerobic and aerobic organisms isolated in infections in women.[2]

Material and methods

Ten patients who had a total of 16 transfusions were managed with intrauterine exchange transfusion by direct intravascular injection. Nine patients had antibodies to Rh_o(D) antigen and were thought to be severely affected on the basis of ultrasonographic findings of hydrops, optical density measurements of amniotic fluid at 450 nm, or both, or severe anemia noted on prior percutaneous fetal blood sampling. The procedure for transfusion was modified according to the technique of Grannum et al.[3] In addition to sedative medications, the patients were administered either 2 gm of cefazolin or 4 gm of piperacillin intravenously immediately before the procedure. The needle was initially inserted into the amniotic cavity and a specimen of amniotic fluid was obtained. The needle then was advanced into the umbilical vein and an initial 3 to 5 ml fetal blood specimen for determination of hematocrit and serum cefazolin levels was obtained. A maternal blood specimen for determination of the maternal serum cefazolin level was obtained at the time of fetal vascular access. Except that specimens were obtained for antibiotic analysis, the exchange transfusions were accomplished as previously described.[3] Hydrops was defined as the presence of an obvious effusion in two or more body spaces. In all cases of hydrops the fetal hematocrit level was <16%.

Amniotic fluid and serum concentrations of cefazolin were determined with paired samples and high-pressure liquid chromatography as described previously.[4] There were no modifications in the acetonitrile dichloromethane phase-extraction procedure, which consisted of 12% acetonitrile and 88% 0.10 mol/L sodium phosphate buffer, pH 6.1. The flow rate was 2.0 ml/min and the detector was operated at 229 nm. The components of the high-pressure liquid chromatography system consisted of a 30 cm C_{18} μBond-a-pak column (Waters Associates, Milford, Mass.), model 6000-A pump, a model 710B Waters Intelligent Sample Processor, and a model 481 detector. Specimens were run in duplicate. Peaks were recorded on a 10 mV chart recorder at chart speed of 0.5 cm/min.

Statistical analysis was performed with Student's *t* test for paired samples. Regression analysis was used to compare the interval from antibiotic administration to sampling and maternal and fetal antibiotic levels.

Results

The results for the patients who received cefazolin are summarized in Table I. There was no correlation between maternal and fetal serum cefazolin levels ($r = 0.012$; $p = 0.973$). The presence of hydrops did not significantly affect the fetal serum cefazolin level. The mean fetal serum cefazolin concentrations in the hydropic and nonhydropic fetuses were 18.0 ± 3.3 and 21.0 ± 17.8 μg/ml, respectively ($t = 0.37$; $p = 0.72$). There was no difference in sampling times of these groups.

As might be expected, the time from antibiotic administration to sampling was correlated with maternal serum of cefazolin level ($r = 0.731$; $p = 0.016$; Fig. 1). As shown in Fig. 2, this relationship could not be demonstrated for fetal serum cefazolin levels ($r = 0.455$; $p = 0.19$); however, the sample size was small. There was a trend for levels to increase with time, suggesting a cumulative transfer effect.

The results for the patients who received piperacillin are summarized in Table II. There were no hydropic fetuses in this group. There was no correlation between maternal serum and fetal serum piperacillin levels ($r = 0.33$; $p = 0.591$). The trend for decreasing ma-

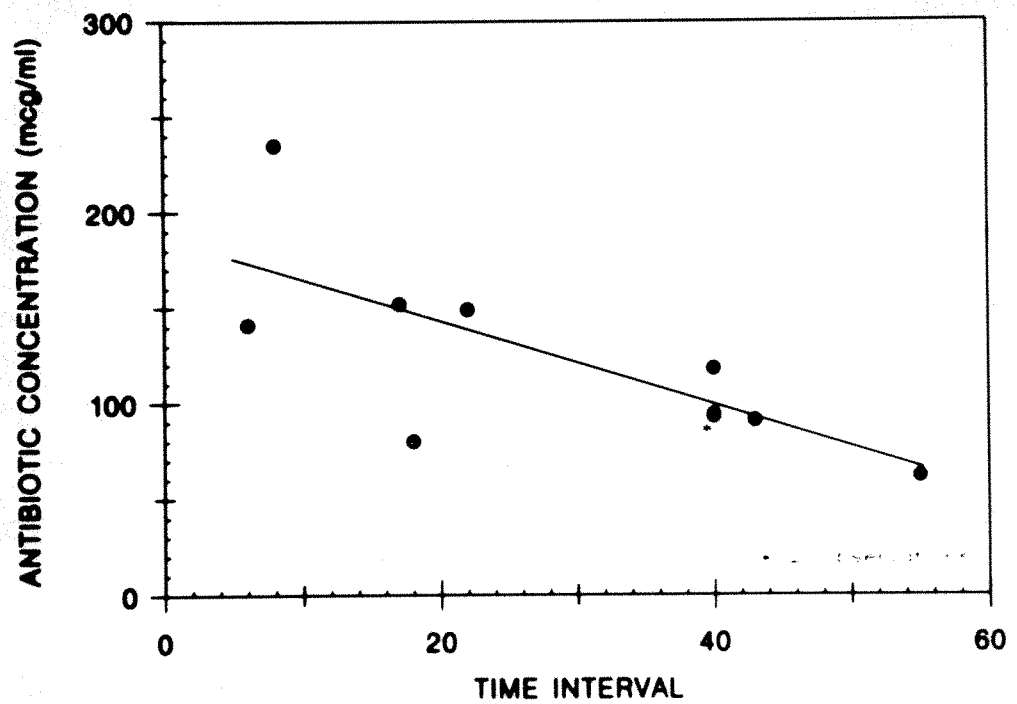


Fig. 1. Maternal serum cefazolin level versus time interval in minutes from maternal drug administration until sample obtained.

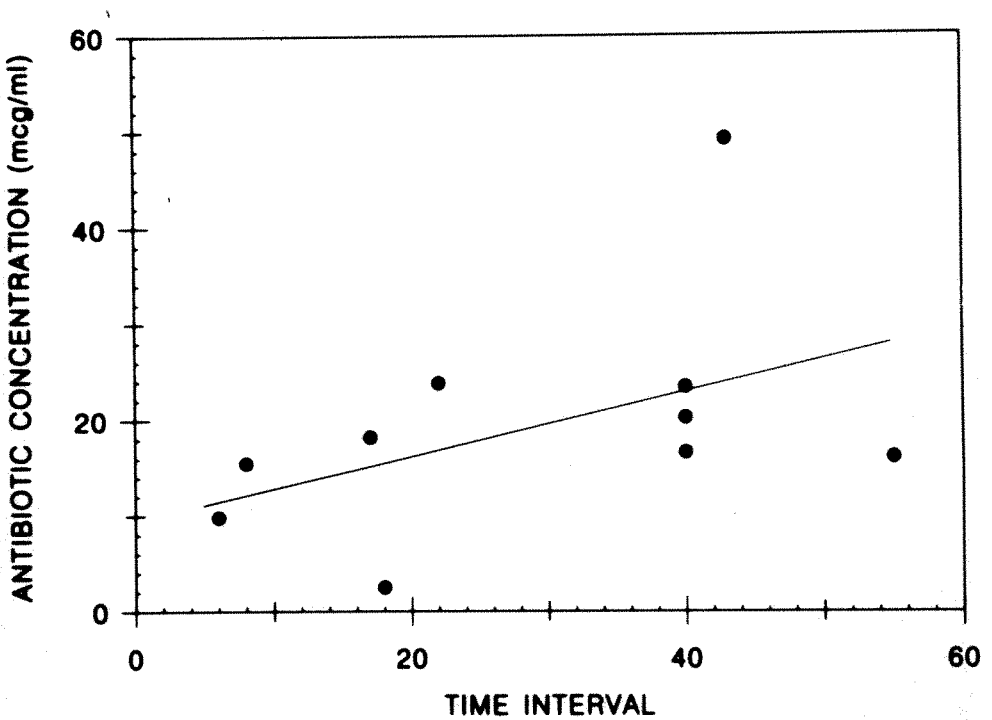


Fig. 2. Fetal serum cefazolin level versus time interval in minutes from maternal drug administration until sample obtained.

ternal and increasing fetal antibiotic level also was seen for piperacillin. There was no statistically significant correlation for either maternal or fetal serum levels with time ($r = -0.567$; $p = 0.24$ and $r = 0.191$; $p = 0.76$, respectively), although the sample size is small.

The amniotic fluid concentration was very low for both cefazolin and piperacillin.

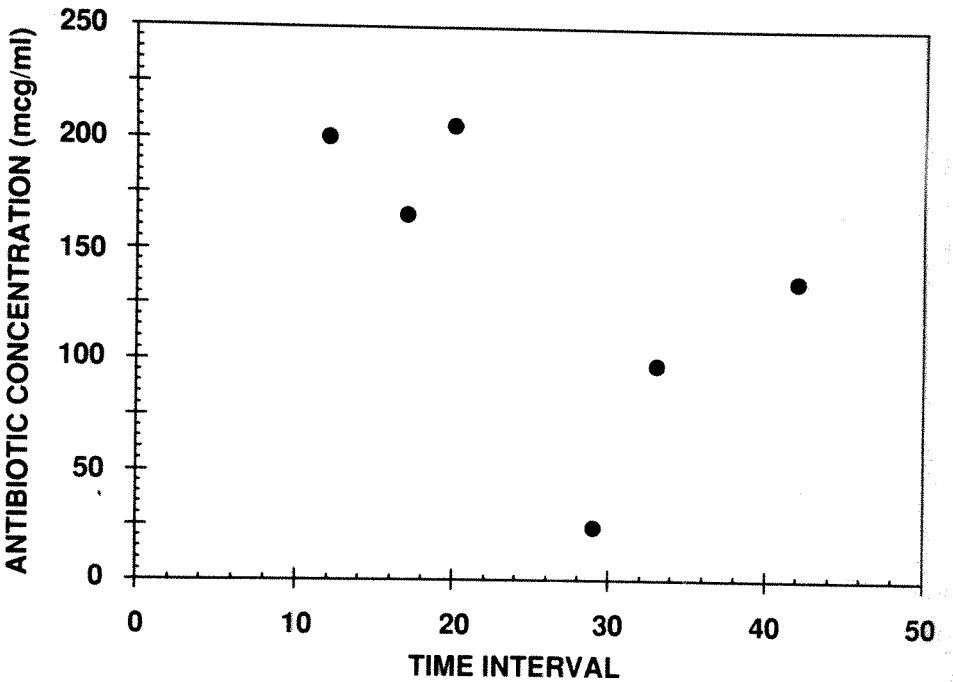


Fig. 3. Maternal serum piperacillin levels versus time interval in minutes from maternal drug administration until sample obtained.

Table II. Summary of piperacillin levels in six intrauterine transfusions

Patient no.	*Procedure*	*Gestational age (wk)*	*Maternal weight (lb)*	*Hydrops present*	*Time to sample (min)*	*Maternal serum (μg/ml)*	*Fetal serum (μg/ml)*	*Amniotic fluid (μg/ml)*
1	1	29	143	–	17	166	21	0.0
	2	32	144	–	29	24	5	0.0
2	1	33	159	–	33	98	40	<1
3	1	22	145	–	42	136	–	0.5
	2	24	147	–	12	201	22	1.7
	3	27	150	–	20	206	23	0.0
Mean + SD						138 ± 69	22 ± 12	0.6 ± 0.7

Comment

Although no clear-cut evidence exists to justify the use of antibiotic prophylaxis for intrauterine transfusions, this has been the practice at Parkland Memorial Hospital for both intraperitoneal transfusions and more recently intravascular transfusions, and is a practice empirically adhered to by others.[1, 5] The organism most often implicated in posttransfusion infection is *Staphylococcus aureus,* which is probably introduced by needle contamination at skin puncture,[5-7] although recently other bacteria have been reported to cause amnionitis afer percutaneous umbilical blood sampling.[8] It has recently been demonstrated at our institution that the level of cefazolin necessary for a mean inhibitory concentration of 90% of isolates was 8 μg/ml for coagulase-negative *Staphylococcus* and 2 μg/ml for *S. aureus* organisms.[9] The mean fetal serum cefazolin concentration clearly met this level; only one determination was less than the 8 μg/ml level for the 90% mean inhibitory concentration of the coagulase-negative *Staphylococcus.*[10] It is of interest that this low level was in a nonhydropic fetus (patient no. 2). This underscores the lack of relationship between the presence of hydrops and transplacental passage of cefazolin.

The fact that there was no difference in placental transfer of cefazolin regardless of the presence of fetal hydrops is of particular interest. Some authors have suggested that hydrops may alter placental transfer of antiarrhythmic drugs.[11] Our data suggest that comparable levels of cefazolin are achieved in all fetuses regardless of the presence or absence of hydrops, although this interpretation is limited because of the small number of patients available for study. Similarly, the level of piperacillin necessary for a 90% mean inhibitory concentration was 16 μg/ml for coagulase-

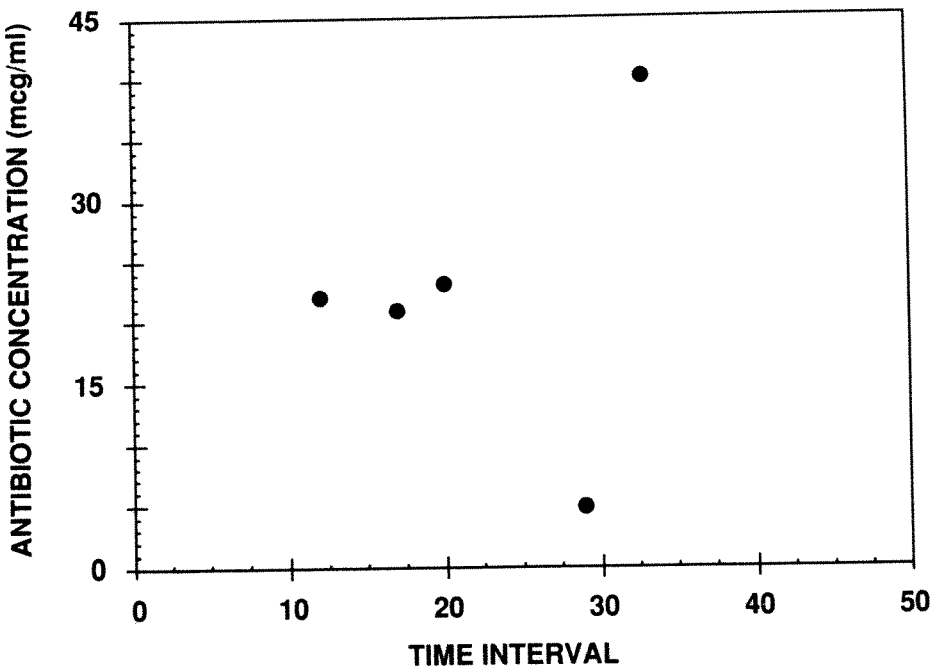


Fig. 4. Fetal serum piperacillin levels versus time in minutes from maternal drug administration until sample obtained.

negative *Staphylococcus* and 16 μg/ml for *S. aureus* in the study mentioned above.[9] This level was rapidly achieved in all but one nonhydropic fetus.

The apparent rapidity of placental transfer is an important issue. It has recently been shown that early antimicrobial treatment of acute chorioamnionitis results in a marked decrease in the incidence of maternal complications and neonatal sepsis.[12] In that series of maternal bacteremia infections and culture-proved neonatal sepsis, all cases were caused by staphylococci or nonenterococcal streptococci, against which cefazolin or extended-spectrum penicillins provide good activity. If placental transport to the fetus is a factor in treatment, we have demonstrated that this occurs rapidly after dosing.

Although our number of observations is limited, the fetal/maternal ratio is approximately 0.16 for both drugs, with adequate levels for *Staphylococcus* being achieved in most cases. Similar results with cefoxitin and mezlocillin have been recently reported.[13] The amniotic fluid concentration was low, although this may increase with time as the fetus has renal clearance of the drugs. This study did not address whether cefazolin or piperacillin prevents transfusion-related chorioamnionitis; however, it did afford the opportunity to evaluate the transplacental delivery of these agents. Because of the rapid placental transfer of these agents, we believe that they may be reasonable agents for the treatment of acute chorioamnionitis even when delivery appears imminent. Further investigation of placental transfer of other antimicrobial agents to determine those with the greatest potential for fetal-neonatal and maternal benefit is warranted.

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Ultrastructural aspects of preeclampsia

II. Mitochondrial changes

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Biopsy specimens were obtained under direct vision at the time of cesarean section from 47 patients (35 with preeclampsia and 12 normotensive patients) and from four women with cesarean section hysterectomies (all normotensive) as an extension of previous work. Tissues were obtained from the myometrium near the placental bed and from the opposite side of the uterus. Skin biopsies were also obtained from eight women with preeclampsia and liver biopsies were obtained from two patients with acute microvesicular fatty change of pregnancy (one with and one without concomitant preeclampsia). Specimens were examined histologically and by electron microscopy. Mitochondrial changes in small vessels, principally venules, in myometrial smooth muscle, myometrial interstitial cells, circulating leukocytes, epidermal and dermal cells, and hepatocytes were examined and compared between women with preeclamptic and normotensive pregnancies. These findings were then compared with mitochondria from 500 biopsies over the same 3-year interval to assess the possible role of delay in tissue fixation. There were 12 other biopsies from nonpregnant women of childbearing age. As further control on artifact, other specimens were initially sampled immediately in the operating room and then serially for up to 2 hours later. Artifact as a basis for the mitochondrial changes was ruled out by these procedures. Normal mitochondria undergo a morphologic conformational sequence with physiologic changes in substrate, oxygen consumption, adenosine diphosphate, and respiratory rate. The mitochondria of preeclamptic tissues show a central disruption that is outside this normal sequence or cycle. This disruption occurs more often and is more severe in preeclampsia than in normotensive pregnancies. In addition, the hypertrophic smooth muscle of the pregnant uterus has a complex of cytoplasmic organelles in a paranuclear location, usually apical, that contains a variable mixture of glycogen, the Golgi apparatus, endoplasmic reticulum, mitochondria, and small unidentified microvesicles. This complex has the location and appearance suggestive of a myometrial "power pack" of significance in metabolism and contraction. The presence of similar mitochondrial changes in a limited sample of nonuterine tissues is suggestive of a systemic metabolic disorder as an important feature of preeclampsia. (AM J OBSTET GYNECOL 1990;163:943-53.)

Key words: Mitochondrial injury, preeclampsia, systemic metabolic effects, cytoplasmic complex of smooth muscle organelles, pregnancy uterine smooth muscle changes

Recent observations,[1-12] including some from our laboratories,[11] have suggested a close relationship between mitochondrial energy states, preeclamptic toxemia (gestosis humanis), familial patterns for preeclampsia, and nutritional and metabolic aspects of pregnancy. The evidence lies in the observation of a pattern of mitochondrial injury[11] that extends beyond the basic cycle of mitochondrial conformational change.[2-4, 6, 8, 9]

It is well established that mitochondria undergo a morphologic conformational sequence with physiologic changes in substrate, oxygen consumption, adenosine diphosphate, and respiratory rate.[2-4, 6, 8, 9] The principal

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6/6/22342



Fig. 1. Small venule, nonplacental region, uterine boundary zone, in patient with severe preeclampsia. Across center field is a crescentic endothelial cell *(E)* with multiple injured mitochondria *(M)* at both ends of the nucleus. In the lower right corner is a similar mitochondrion *(Mi)* in a circulating segmented neutrophilic leukocyte. (Original transmission electron microscopic magnification, ×5000.)

forms are *orthodox* (an open pattern with cristae) and *condensed* (a noncristal matrix with inner spaces). State 1 is characterized by an increased density of the cristae correlated with a low substrate and adenosine diphosphate energy state and with a slow respiratory rate (the condensed conformation) through an open or orthodox pattern during which phosphorylation of adenosine diphosphate occurs.[2] Subsequent states 2 through 5 have systematic but independent variations in substrate, adenosine diphosphate level, respiratory rate, and oxygen content that are not always coordinated with oxidative phosphorylation; these states have variable time courses and mixes of the condensed and orthodox conformations.[2] The details are beyond the scope of this article and will be discussed in a future article.

The injury pattern reported in this study has features more closely identified with particular aspects of the



Fig. 2. Interstitial oncocytic cell of myometrium near term in a normotensive patient. Note extreme crowding of mitochondria, including a large one *(X)* in the lower field. Cristae are not always complete and not always symmetric, but the differences from preeclamptic mitochondria are often very striking and obvious. (Original transmission electron microscopic magnification, × 16,000.)

mitochondrial energy cycle, specifically postcalcium release phosphate-dependent matrix change, which leaves a membrane whorl[4] as a marker of the preceding events.

The endothelium of small uterine vessels in preeclampsia often has a diffusely swollen cytoplasm, and the mitochondria commonly rupture into the cytosol or vascular lumen.[11]

The purpose of this article is to describe and compare mitochondrial changes in normotensive and preeclamptic pregnancies as an extension of our previous work.[11]

Material and methods

Informed consent for placental bed and uterine boundary, liver, and skin biopsies was obtained from various patients in the prenatal clinics of the E. H. Crump Hospital who were scheduled for cesarean sec-

tion on obstetric or perinatal grounds. A total of 47 patients, 35 with preeclampsia (systolic blood pressure >140 torr, diastolic blood pressure >90 torr, or both, with proteinuria >300 mg/24 hr), and 12 normotensive women had biopsies. Four cesarean section hysterectomy biopsy samples from normotensive patients were studied, for a total of 51 patients (16 normotensive and 35 hypertensive). At the time of cesarean section biopsy specimens approximately 0.8 × 0.6 × 1.0 cm were excised by sharp dissection and were immediately placed in the appropriate fixative. Placental site samples were taken to include underlying myometrium just after placental removal, and comparable nonsite samples were taken from the opposite uterine wall. Liver and skin biopsies were taken in accordance with ordinary surgical procedures. On receipt in the pathology laboratory appropriate accession numbers were assigned and the samples were trimmed into pieces for paraffin or plastic embedding according to standard techniques, beginning with 10% neutral-buffered aqueous formalin for histology and net 1.0% glutaraldehyde-buffered in Sorenson's solution for ultrastructural study.

Paraffin sections were cut at 5 μm and were stained by hematoxylin and eosin for light microscopy. Histologic preparations were available for all 51 patients.

Plastic sections for electron microscopy were prepared in the usual manner with lead acetate staining of thin-cut sections at 0.4 μm. Electron micrographs were taken at × 1600 to × 25,000 original magnification with a Zeiss EM-10C electron microscope and were printed at an average additional enlargement of 2.7 times. Transmission electron micrographs were available for 29 of 35 women with preeclampsia and for 13 of the 16 normotensive patients.

During these studies two patients with acute microvesicular fatty liver of pregnancy (one with and one without concomitant preeclampsia) had liver biopsies as part of their diagnostic workup. Both biopsies were studied by electron microscopy. Preliminary observations indicated the need to examine tissues other than uterus. Accordingly, skin biopsies were also obtained from eight women with preeclampsia at the time of cesarean section delivery. These findings were compared with mitochondria in 500 electron microscopy biopsies over the same 3-year interval to assess the possible role of delay or artifact in tissue fixation. Twelve of these samples were from nonpregnant women of childbearing age. As further control of artifact, several other specimens were initially sampled immediately in the operating room and then serially for up to 2 hours later. Artifact as a basis for the mitochondrial changes was ruled out by these procedures.

Results

Mild, focal mitochondrial changes were observed in some normotensive specimens. Because there was a marked progression of both number and severity of injured mitochondria in women with preeclampsia, the initial change can be considered an effect of underlying metabolic adaptation or stress from pregnancy itself.

The earliest change was a clearing within the matrix of the mitochondria that appeared as a zonal loss of cristae, usually eccentric. This change in mitochondria resembled condensed deenergized state 5[2, 3, 6, 8] but lacked the discrete folds of the matrix and the previously described "buttonhole" openings[2, 3, 6, 8] in the dense zones. This clearing became larger and sometimes the mitochondrion bulged distinctively. Cristal material was then compressed against the lateral membrane and some ghost cristae become apparent. Another severe form occasionally seen in the preeclamptic group was a diffusely enlarged mitochondrion, up to twice the normal size, that basically resembled energized state 4,[2, 3, 6, 8] but with cristae bent against the lateral membrane. In these more advanced forms a laminated roll or whorl was seen. This pattern has been identified as a remnant feature of postphosphate calcium release in state 6.[4] These changes were present in small uterine and cutaneous vessels, in both smooth muscle and the interstitium of the myometrium, in circulating leukocytes, and in parenchymal skin cells, indicating a systemic change. The liver mitochondria in one patient with both preeclampsia and microvesicular fatty change showed mild injuries of a similar type, but these were changes not seen in the liver biopsy of one patient without preeclampsia. Another general observation from these samples is that mitochondria in the several sites have a different overall appearance. Liver mitochondria have a more typical orthodox configuration, whereas those elsewhere tend to have a condensed appearance.

Vascular endothelial changes. The specific changes included markedly swollen mitochondria that bulge, sometimes into the vascular lumen with resultant rupture and release of their contents, a prelude to endothelial erosion.[11] Another special feature is that diffuse cytoplasmic swelling is seen; this occurs infrequently in normal pregnancy and much more often and more severely in preeclampsia.[11] This is an alternate pathway to erosion. Some random electron micrographs have shown both mitochondrial and diffuse cytoplasmic swelling in endothelial cells of preeclamptic biopsy specimens. Injured mitochondria were either quite isolated or clustered. The clusters usually showed a range of mitochondrial size and degree of injury (Fig. 1). Several electron micrographs of placental site and elsewhere showed similar mitochondrial changes in circulating leukocytes (Fig. 1).

Myometrium. Mitochondria are found in both myometrial smooth muscle and in various interstitial cells. Some of the latter are oncocytic; that is, they have large numbers of mitochondria. In normotensive pregnancy



Fig. 3. Apical location of myometrial paranuclear complex (nucleus, *N*). Complexes vary in relative amounts of glycogen *(G)*, mitochondria, Golgi, and endoplasmic reticulum *(E)*. In this example the complex is small in this plane, with closely packed endoplasmic reticulum below and some glycogen to the right. Seven mitochondria are present (three are labeled, *m*) and all have a centrally cleared zone. (Original electron microscopic magnification, ×6000.)

these have an orthodox configuration (Fig. 2). The mitochondria of myometrium vary in number and size, but in muscle cells that show gestational hypertrophy they are in paranuclear locations, often apical, where they are mingled with the Golgi apparatus and deposits of glycogen (Figs. 3 to 5). Most smooth muscle mitochondria are found in the paranuclear complex. These mitochondria show the same type, range, and degree of changes described above. Extreme magnification shows some mitochondria to be only zonally injured, whereas others are recognizable as mitochondria only from a few remnant cristae and the double outer envelope (Fig. 5).

Skin

Similar mitochondrial changes were found in dermal connective tissue cells, in epidermal germinal layer cells (Fig. 6), in leukocytes of preeclamptic specimens, and in skin vessels.

Liver

Liver biopsies for diagnosis of microvesicular fatty change (Figs. 7 and 8), a metabolic disorder with some features of Reye's syndrome, also show mitochondrial injury in preeclampsia (Fig. 8) but present an orthodox appearance when the microvesicular lesions occur alone (Fig. 7). The extent to which either lesion might

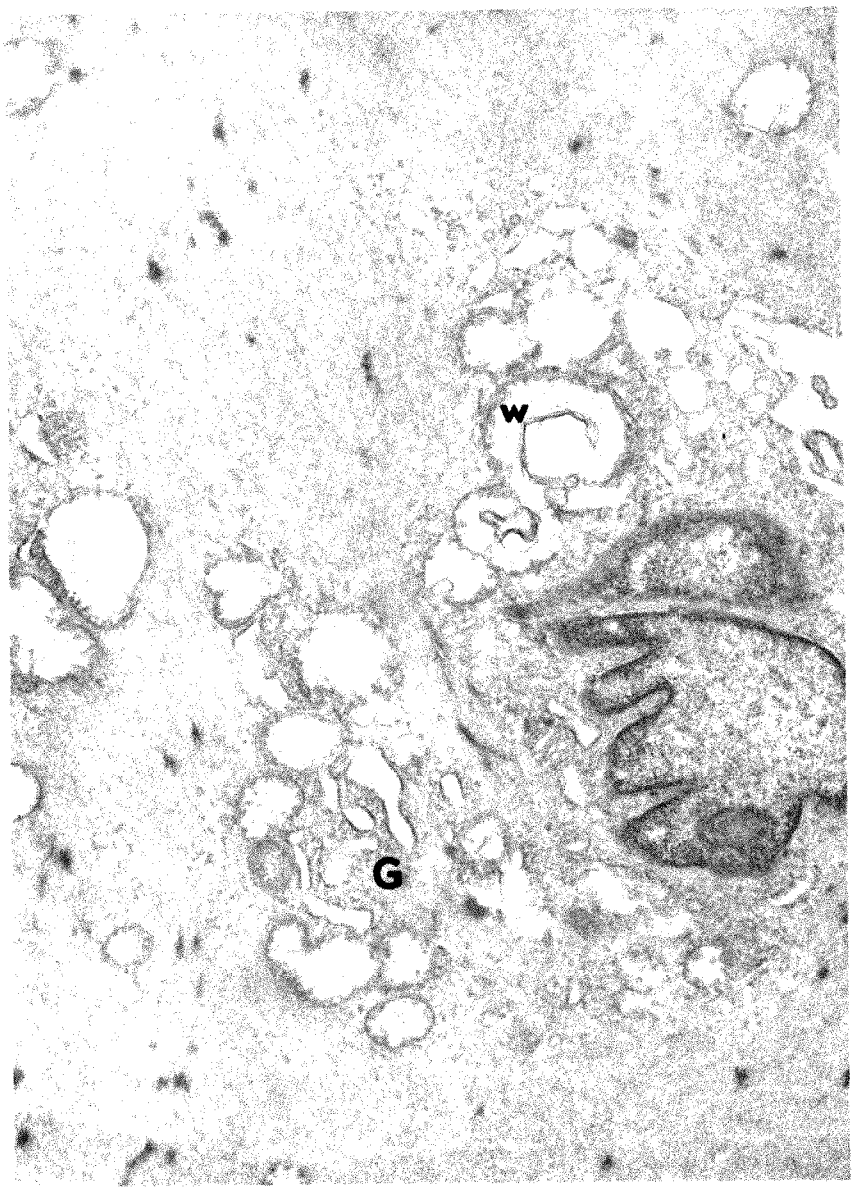


Fig. 4. Apical location of larger myometrial paranuclear complex. Advanced injury to mitochondria in severe preeclampsia with "whorls" *(W)* within cleared mitochondria *(center)* and moderately dilated tubular Golgi *(G)* irregularly displayed about the complex. There is light stippling of glycogen close to the tip of the nucleus and within the complex below and to the left. (Original transmission electron microscopic magnification, ×8000.)

influence the appearance or functional severity of the other is unclear from this limited ultrastructural survey. However, it does serve to show another systemic aspect of the mitochondrial changes in preeclampsia.

Comment

Because cell vitality is dependent on intact mitochondria capable of the cyclic sequence of reconformation, with all the metabolic and energy transfer implications that reconformation portends,[2-4, 6, 8, 9, 12] pathologic deviations of the type described in this study are evidence of a potentially profound metabolic disturbance. The metabolic implications of preeclampsia might be best assessed from within closely controlled studies on pregnancy nutrition,[10] with special reference to two different but likely integrated lines of consideration: the competency of the protein matrix of the mitochondrion[5, 12] and the energy reserves and nutrient

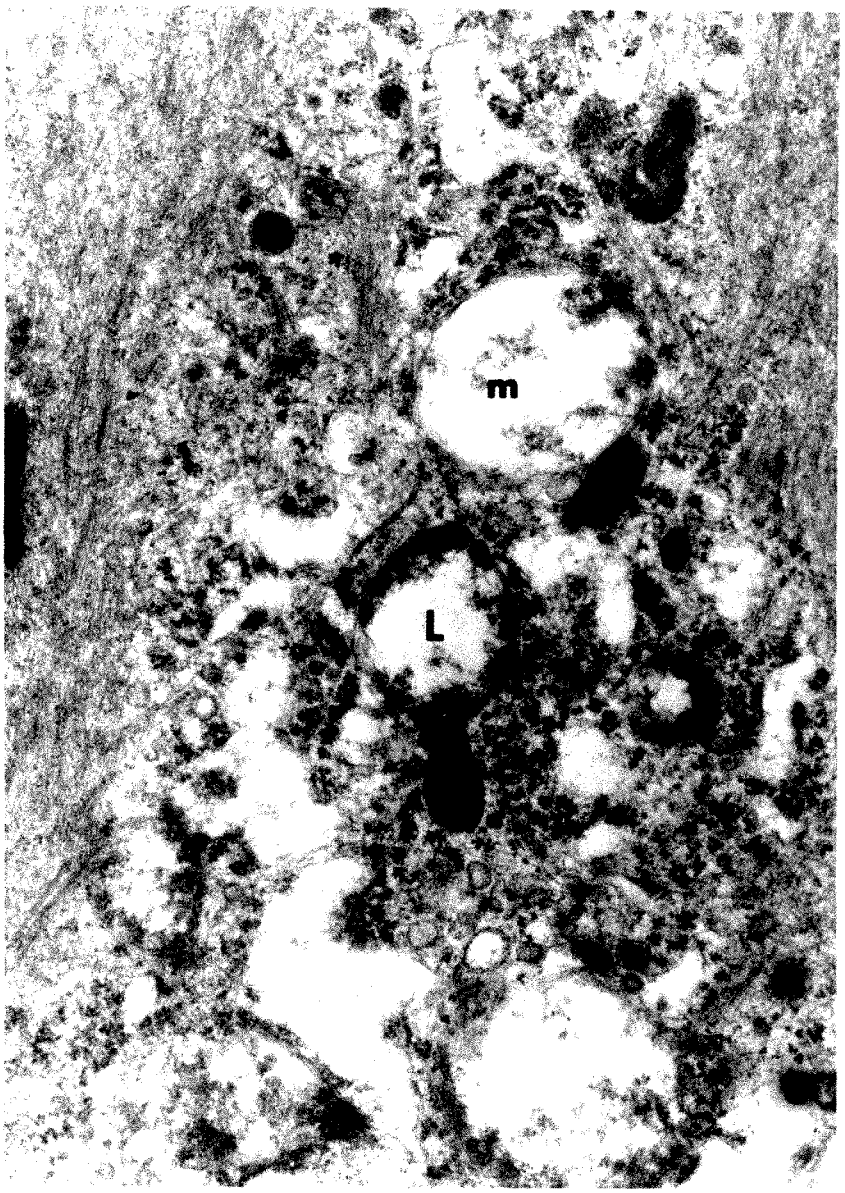


Fig. 5. Biopsy specimen of patient with severe preeclampsia shows mitochondrial injury in a myometrial apical paranuclear complex. Note moderate deposit of granular glycogen. The dumbbell-shaped mitochondrion *(L)* just below the center is only partially cleared. Immediately above it is another, somewhat larger mitochondrion with few cristal remnants *(m)*. (Original transmission electron microscopic magnification ×16,000.)

requirements for healthy evolution of the pregnancy, including fetal growth and maturation.[10] The former point is clearly related to the amino acid pool drawn from the initial maternal reserves and subsequent food intake, especially during the period of most rapid uterine and fetal growth.[10] Maintenance of mitochondrial integrity, like that of other aspects of cell machinery, is dependent on the proteins and enzymes necessary and available at the time of organelle renewal. The second point derives from the relationship between the energy costs of pregnancy and the conversion efficiency of maternal cells and tissues that lie between ingested food and the fetal side of the placental barrier.[10] It is not possible from present observations of these mitochondria to focus more specifically on the metabolic or nutritive aspect most involved in their injury.

The finding of a paranuclear complex in uterine smooth muscle that contains the principal parts of a

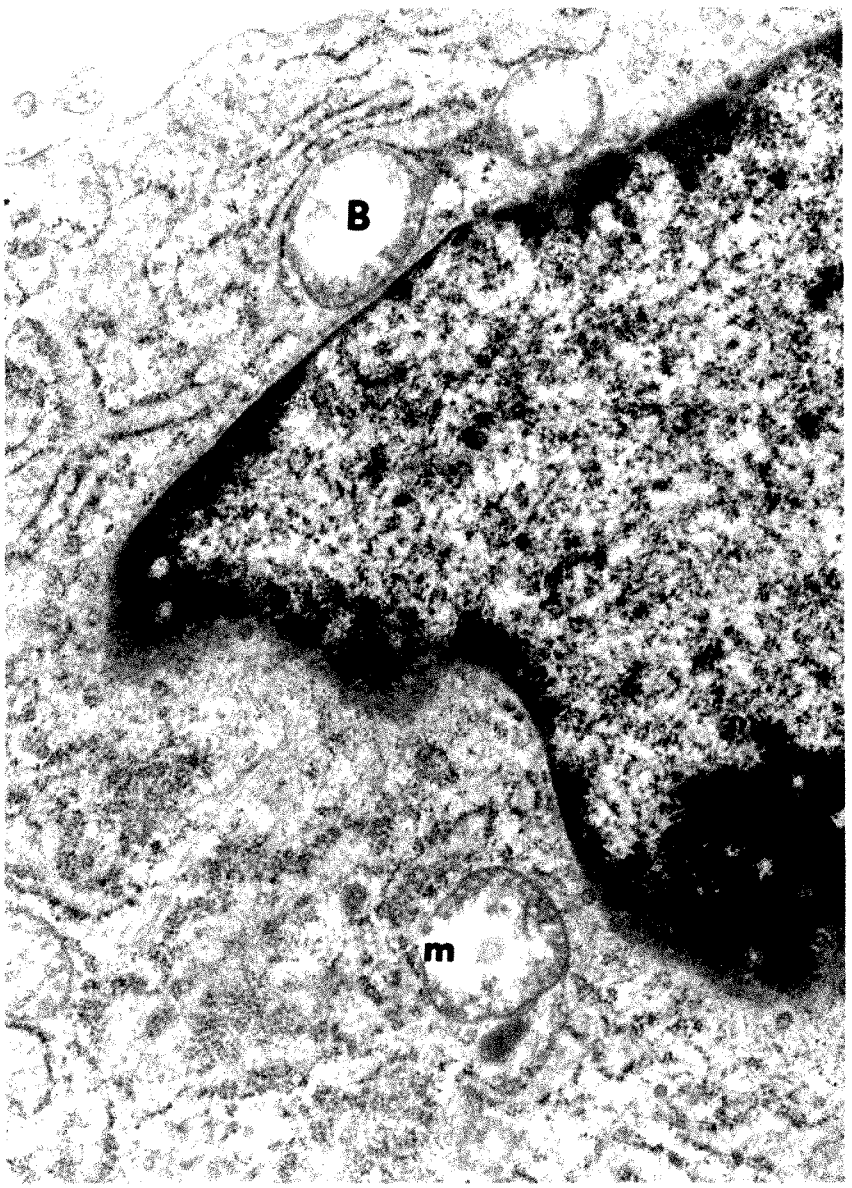


Fig. 6. Sample from patient with severe preeclampsia depicts mitochondrial injury in germinal layer of epidermis. Lower mitochondrion *(m)* has a small contained "whorl," and the dumbbell-shaped upper mitochondrion *(B)* has cavitary change in both lobes. (Original transmission electron microscopic magnification, ×12,000.)

bioenergetic engine, mitochondria, Golgi, glycogen, and endoplasmic reticulum (Figs. 3 to 5) serves as a possible line of further investigation into the pathogenesis of gestosis. It has already been noted that aerobically active organs with a high demand for adenosine triphosphate, such as brain, retina, and cardiac and skeletal muscle, are especially vulnerable to the effects of mitochondrial disorder.[5-7] We suggest that the pregnant uterus is a similar high metabolic zone and that it may qualify for pathophysiologic problems in a similar fashion. The examples we have illustrated (Figs. 3 to 5) are only a small part of the overall range of the paranuclear complex. In some cases they extend along the nucleus and become biapical, in others the complex is much larger. Generally, but not exclusively, the larger complexes have more glycogen. This factor might relate the fundamental development of the complexes to the ultimate functional adequacy of the uterine unit.

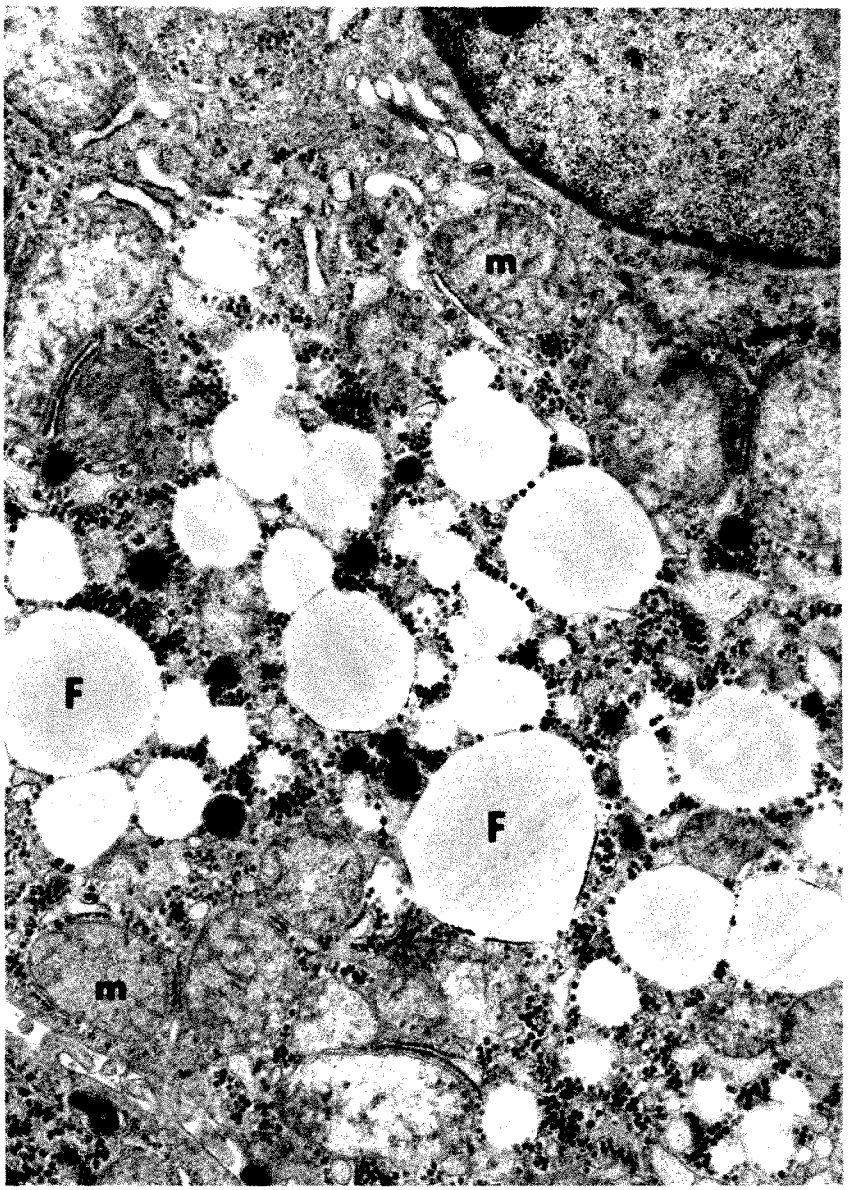


Fig. 7. Liver biopsy specimen of a 37-year-old woman (gravida 5, para 3, abortions 1) with recurrent microvesicular fatty change of pregnancy *(F)* but no preeclampsia. The fatty deposits are at least partially membrane bound with many nearby granules of glycogen. Mitochondria *(m)* are orthodox with somewhat irregular cristae but no cavitation. (Original transmission electron microscopic magnification, ×8000.)

This in turn may well be a consequence of genetic capacity. Clearly more work is needed on this aspect of these observations, especially with regard to possible correlations between the degree of ultrastructural change and the intensity or severity of the clinical syndrome.

One factor to consider with regard to genetics in the occurrence of preeclampsia is a tendency toward familial manifestations.[1] If there is a genetic component to preeclampsia, it is a singular one since the overt manifestations of whatever the underlying lesion or fault might be are seen only in women. Mother-to-daughter inheritance might be enhanced regularly if it were based on mitochondrial genetics, which are matrilineal[5] even though there is a definite regulatory or interactive role for nuclear deoxyribonucleic acid at very basic levels in the expression of the mitochondrial genome.[12] Such thoughts compel a possibly unasked

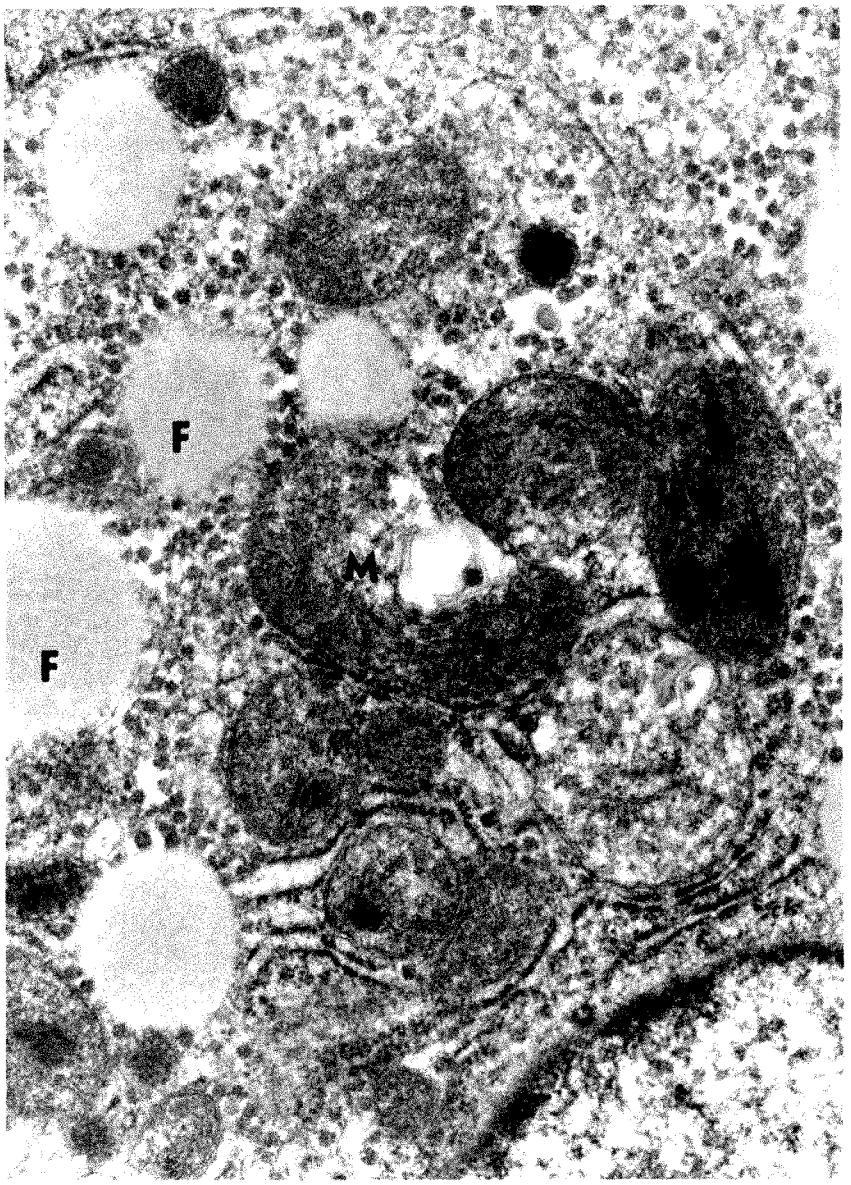


Fig. 8. Liver biopsy specimen of a 20-year-old primigravid woman with moderate preeclampsia; microvesicular fatty change *(F)* and mild central mitochondrial injury *(M)*. (Original transmission electron microscopic magnification, × 16,000.)

question: What are the metabolic expressions of mitochondrial lesions in the male offspring of mothers with preeclampsia?

This study is projective and qualitative, not quantitative. Additional studies are planned to determine more precisely the range, size, frequency, and internal constellation of the paranuclear complex. We also anticipate examining the manner by which and the extent to which the mitochondrial injuries we have described correlate with this structure that contains almost all of the mitochondria of uterine smooth muscle.

We thank Deborah Hollis for preparation of tissues for electron microscopy and Frank Moretta for the electron micrographs.

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Absence of evidence of pulmonary maturity at amniocentesis in term infants of diabetic mothers

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A total of 153 patients' charts were reviewed over a 6-year period to assess the results of the practice of amniocentesis for diabetic mothers at term (≥37 weeks' gestation) before elective induction/delivery. The numbers of cases with absent phosphatidylglycerol were determined at each specific gestational age at or near term. Phosphatidylglycerol was present in 130, and phosphatidylglycerol was absent in 23 at first amniocentesis sampling. A significant proportion (~21%) of those with gestational diabetes were phosphatidylglycerol–negative as late as 38 weeks' gestation. A similar proportion of overt diabetic patients were phosphatidylglycerol–negative as late as 39 weeks' gestation. These figures give the clinician some estimate of the likelihood of the absence of phosphatidylglycerol at or near term if amniocentesis is used before elective delivery in these patients. (Am J Obstet Gynecol 1990;163:954-7.)

Key words: Diabetes, amniotic fluid, phosphatidylglycerol, term

Many investigators have shown that maternal diabetes may adversely affect the process of fetal lung maturation.[1-7] Hyperglycemia and hyperinsulinemia have been implicated in delayed lung maturation in fetuses of diabetic mothers, but the precise mechanisms are still being investigated. Infants of diabetic mothers are known to have an increased incidence of respiratory distress syndrome (RDS).[8-12] Phosphatidylglycerol is a phospholipid that appears in significant amounts in amniotic fluid starting at about 36 to 37 weeks' gestation.[13-16] It has been used as a marker for lung maturation, and its appearance may be delayed in diabetic pregnancies with its absence being associated with RDS in some cases, despite a mature lecithin/sphingomyelin ratio.[17-19] For this reason, diabetic mothers who do not go into spontaneous labor at term routinely have amniocentesis done at many institutions, including ours, to determine the presence or absence of phosphatidylglycerol before elective induction/delivery. Our objective was to determine the frequency with which this practice yielded results that do not show pulmonic maturity.

Material and methods

A total of 153 charts of diabetic mothers who were delivered of infants at our center between February 1983 and January 1989 were reviewed. During that time period most pregnant women with diabetes were allowed to go into labor spontaneously, but those whose cervix was judged to be favorable for induction at or beyond 37 weeks' gestation were offered amniocentesis for assessment of fetal lung maturity and induction of labor if phosphatidylglycerol was present. Of our diabetic population 9.6% (153 of 1600) had amniocentesis for elective induction of labor or cesarean section at term during the study period; this included 7.3% (103/1415) of patients with gestational diabetes mellitus and 27% (50/185) of overt diabetic patients. The inclusion criterion was amniocentesis performed at ≥37 weeks' gestation. Patients were assigned to gestational diabetes (n = 103), overt diabetes type I (n = 27), and overt diabetes type II (n = 23) groups. Some were managed in our diabetic clinic and others by their private obstetricians.

All subjects had undergone transabdominal amniocentesis for fetal lung maturity before elective induction/delivery at term and were delivered in our hospital. When phosphatidylglycerol was absent, amniocentesis was repeated at a 7-day interval unless the patient declined repeat amniocentesis. Patients who had rupture of membranes before amniocentesis were excluded. Gestational age was determined on the basis of menstrual dates confirmed by ultrasonography in the majority of the patients. Elective delivery was deferred until phosphatidylglycerol was present.

We looked only at the first amniocentesis sample of each patient to eliminate bias that might be introduced by repetitive sampling. The numbers of cases with absent phosphatidylglycerol were determined at specific gestational ages or at near term.

Phosphatidylglycerol was determined by a two-

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dimensional thin-layer chromatography method similar to that described by Kulovich et al.,[20] as described below. The sensitivity of the assay for phosphatidylglycerol is 0.025 mg/L. After centrifugation at 1600 rpm for 10 minutes, 5 ml of amniotic fluid supernatant in a mixture of chloroform and methanol (10/5, vol/vol) was centrifuged at 2000 rpm for 10 minutes on the day of collection. Specimens were stored at −20° C after centrifugation if specimens were to be run the next day. Cold acetone (0.75 ml) was used to precipitate the extracted phospholipids by centrifuging for 3 minutes at 2000 rpm. The extracted phospholipid (the unknown) was allowed to dry and then was reconstituted with 35 μl of chloroform. Precoated plates with silica gel 60 were used for the two-dimensional thin-layer chromatography. A standard that consisted of 0.025 mg/L of standard phosphatidylglycerol (P0514, Sigma, St. Louis) was used. Solvent I was made up of chloroform, methanol, glacial acetic acid, and water (65/25/8/4, vol/vol/vol/vol). Solvent II was made fresh each day of tetrahydrofuran, methylol, methanol, and 0.57 N ammonium hydroxide (50/37/8/5.25, vol/vol/vol/vol). Plates were removed, allowed to dry, placed in an iodine tank until the spots were visible, and then read.

Circulating glucose levels recorded during the third trimester were available for 61 subjects. Glucose levels were capillary whole blood samples measured on reflectance meters. Meter accuracy was verified by intermittent simultaneous capillary tube blood glucose measurements. Mean daily values were derived by averaging all measurements (fasting and 2 hours after each meal) obtained during the third trimester.

The group glucose means were derived by averaging all the means of the persons in each group, and were compared with the unpaired Student *t* test. Differences in prevalence of the absence of phosphatidylglycerol were compared with χ^2 analysis.

Results

A total of 130 diabetic mothers had phosphatidylglycerol present and phosphatidylglycerol was absent in 23 at first sampling at term. Of the 23 subjects with the absence of phosphatidylglycerol, 11 had gestational diabetes, seven had type I diabetes, and five had type II diabetes. The mean gestational age for the phosphatidylglycerol–negative group was 37.6 ± 0.7 weeks and that for the phosphatidylglycerol–positive group was 38.3 ± 1 weeks (p = NS). Phosphatidylglycerol was absent in ~26% of subjects at 37 weeks, ~20% at 38 weeks, ~4% at 39 weeks, and none at 40 weeks' gestation (Fig. 1).

When subjects were analyzed according to type of diabetes (Fig. 2), a significant proportion (~21%) of those with gestational diabetes were

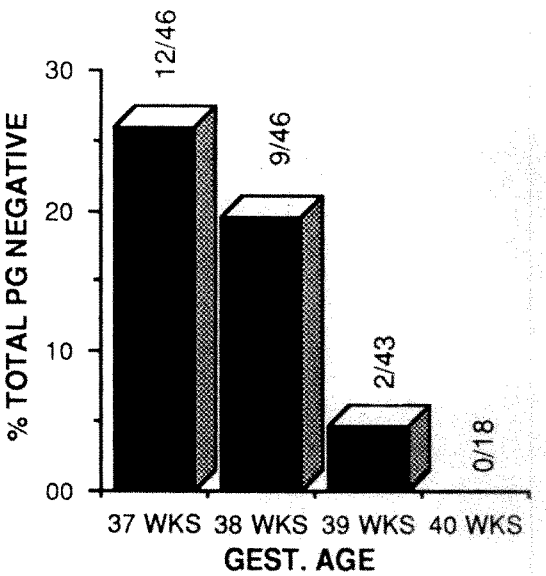


Fig. 1. Total number of diabetic mothers with absence of phosphatidylglycerol at each gestational age at first sampling. *PG*, phosphatidylglycerol.

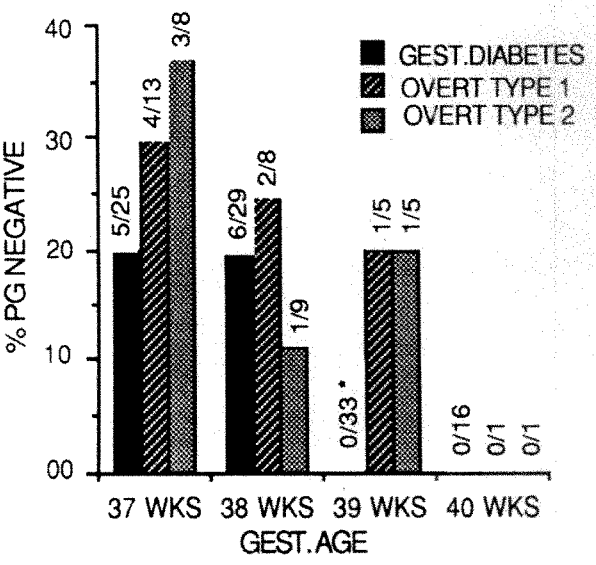


Fig. 2. Proportion of patients with various types of diabetes with absence of phosphatidylglycerol at each week of gestation near term. *PG*, phosphatidylglycerol.

phosphatidylglycerol–negative as late as 38 weeks' gestation. A similar proportion of women with overt diabetes were phosphatidylglycerol–negative at 39 weeks' gestation.

Comparison of the proportions of patients with gestational diabetes and overt diabetic mothers with the absence of phosphatidylglycerol did not show any significant difference until 39 weeks' gestation as shown in Fig. 2.

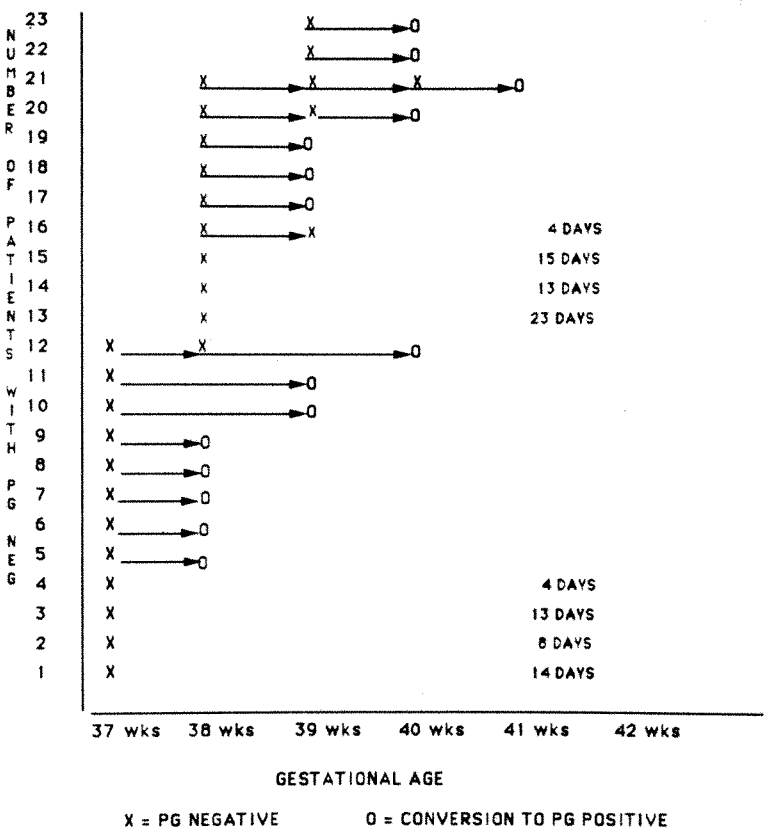


Fig. 3. Follow-up of subjects who were phosphatidylglycerol–negative at first sampling. Number of days denotes time elapsed from last amniocentesis to delivery. *PG*, phosphatidylglycerol.

Table I. Mean blood glucose levels in third trimester

Group	*No.*	*Mean*	*SD*
Phosphatidylglycerol negative	13	96.8 mg/dl	±9.9
Phosphatidylglycerol positive	48	100.6 mg/dl	±11.6

p = NS.

Of the 23 subjects with the absence of phosphatidylglycerol at or near term, phosphatidylglycerol developed in 15 with subsequent repeat amniocenteses. The other eight went into spontaneous labor and were delivered of infants before phosphatidylglycerol was shown to be present, but only two of these were delivered within 4 days of the documented absence of phosphatidylglycerol. The other six were delivered of infants within 8 to 23 days (Fig. 3). RDS did not develop in any infant.

We did not exclude diabetic mothers with other medical complications of pregnancy. However, 83 (64%) of the 130 diabetic mothers with amniotic fluid phosphatidylglycerol–positive and 15 (65%) of the 23 diabetic mothers with the absence of phosphatidylglycerol had no other medical conditions complicating their pregnancies. Twenty-six (20%) of the 130 diabetic subjects with positive phosphatidylglycerol and four (17%) of the 23 subjects with the absence of phosphatidylglycerol had infants ≥4000 gm. The degree of metabolic control of both groups was similar (Table I). When patients with gestational diabetes and overt diabetes who were phosphatidylglycerol–positive and phosphatidylglycerol–negative (and for whom glucose values were available) were compared separately, the degree of metabolic control was not significantly different.

Comment

Pregnancy duration is the most important factor in the determination of the presence or absence of phosphatidylglycerol in amniotic fluid at term in diabetic mothers. Our limited blood sugar data seem to support the findings of Ferroni et al.,[21] that diabetic blood glucose control had no significant effect on the amniotic fluid phospholipid levels. However, our subjects were generally in good metabolic control and none of those with the absence of phosphatidylglycerol had mean blood glucose levels ≥110 mg/dl. Landon et al.[22] had one White class B and two class D diabetic patients with

the absence of phosphatidylglycerol at 37 and 38 weeks' gestation, respectively, among subjects with mean capillary blood glucose levels ≥110 mg/dl, whereas in our study phosphatidylglycerol was absent in ~20% of overt diabetic patients as late as 39 weeks' gestation even though all available mean capillary blood glucose levels were ≤110 mg/dl. In our population of pregnant women with diabetes, a significant proportion of fetuses could not be documented to have pulmonic maturity at 38 to 39 weeks' gestation. We chose not to include the result of repetitive sampling on the same persons in our data anlaysis to avoid biasing a cross-sectional study with longitudinal data. Nevertheless, it should be noted that one person first sampled at 38 weeks' gestation did not convert to phosphatidylglycerol–positive status during weekly samplings until 41 weeks' gestation (Fig. 3).

Our study could not evaluate the prevalence of RDS among infants of diabetic mothers at term because patients were not electively delivered if phosphatidylglycerol was absent. Lack of phosphatidylglycerol is not invariably associated with RDS. Thus it should not be assumed that RDS will develop in 20% of infants of mothers with gestational diabetes or overt diabetes if electively delivered at 38 to 39 weeks' gestation. For clinicians who depend on phosphatidylglycerol for elective delivery in diabetic pregnancy, this compound may be absent in a significiant proportion of cases until 39 weeks' gestation is reached. The benefit of amniocentesis in well-controlled diabetic patients beyond 39 weeks' gestation remains debatable.

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Liver histopathologic findings in women with sickle cell disease given prophylactic transfusion during pregnancy

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Forty women with a major sickle hemoglobinopathy (hemoglobin SS, SC, or S–β-thalassemia) were given red blood cell transfusions prophylactically during pregnancy. A mean of 13.6 units of erythrocytes per woman was given and none received more than 28 units. Direct-vision needle biopsy of the liver was performed in conjunction with cesarean section or puerperal sterilization. Although iron deposition in hepatocytes and Kupffer cells was identified commonly, neither cirrhosis nor widespread hepatocellular necrosis was found. We conclude that the risk of irreversible hepatic damage is negligible in women with sickle hemoglobinopathies who are given erythrocytes prophylactically during one pregnancy. (Am J Obstet Gynecol 1990;163:958-64.)

Key words: Sickle cell disease, pregnancy, prophylactic blood transfusions, liver histopathology

In 1971, investigators from Memphis[1] concluded that the risk of pregnancy for women with sickle cell disease was prohibitively high. Two years later, workers from Dallas[2] reported more favorable pregnancy outcomes although maternal morbidity and mortality still were significant. After the latter report from Parkland Hospital, we adopted a policy of prophylactic red blood cell transfusions for women with major sickle hemoglobinopathies (SS, SC, S–β-thalassemia). From our clinical experiences, which span nearly two decades,[3, 4] as well as those of others,[5] it is clear that both maternal and perinatal outcomes have improved dramatically with prophylactic transfusions. However, because these studies were not randomized and controlled, the singular importance of prophylactic transfusions was not established, and indeed, in a recently reported randomized investigation, it was concluded that such transfusions could be safely omitted.[6] Thus prophylactic red blood cell transfusions for pregnant women with sickle hemoglobinopathies remain controversial.[7] Undoubtedly a major factor militating against such therapy is transfusion-related morbidity, and one concern is that iron overload, or transfusion hemosiderosis, will cause irreversible damage to the liver or to other organs.[8] To better define this risk of erythrocyte administration, we performed intraoperative liver biopsy in 40 women with sickle hemoglobinopathies at the conclusion of a pregnancy during which each was transfused prophylactically.[3, 4]

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6/6/22315

Material and methods

Beginning in 1973, all pregnant women with a major sickle hemoglobinopathy (hemoglobin SS, SC, or S–β-thalassemia) who received prenatal care at Parkland Memorial Hospital were offered prophylactic red blood cell transfusions. As described in detail previously,[3, 4] packed red blood cells were given in volumes sufficient to achieve a hematocrit >25% and a percentage of cells containing sickle hemoglobin of ~50%. Because of the inherent risks of both transfusion therapy and the underlying disease, women participating in the protocol were counseled to consider permanent sterilization. Consent was obtained for a direct-vision needle biopsy to be performed either at the time of cesarean section or with puerperal sterilization done soon after vaginal delivery. All biopsies were performed within 4 weeks of the last transfusion, and in no case was percutaneous liver biopsy performed.

Immediately after biopsy, the histologic specimen was placed in formalin. Sections were cut, mounted, stained with hematoxylin-eosin, Masson trichrome, and Prussian blue, and graded microscopically in a systematic manner similar to that previously described[9] for the following features: (1) preservation or disruption of normal lobular and sinusoidal architecture; (2) hepatocellular necrosis, regeneration, iron deposition, and the presence of fat, lipofuscin, and bile inclusions; (3) portal tract fibrosis, cirrhosis, inflammation, and marginal disruption; (4) sinusoidal dilation and congestion,

Table I. Clinical data from 40 women undergoing prophylactic red blood cell transfusions

Factor	*Hemoglobinopathy*		
	SS hemoglobin	*SC hemoglobin*	*S–β-thalassemia*
No. of women	22	16	2
Mean gestational age at first transfusion (wk)	17	21	17
No. of units transfused			
Mean	13	14	13.5
Range	5-22	3-28	12-15
Aspartate aminotransferase			
<100 U/L	13	14	2
>100 U/L	5	1	0

erythrophagocytosis, and fibrosis; and (5) iron deposition in Kupffer cells. The stainable iron was graded as 0 if there were none or only rare granules in a few cells. Grade 1+ showed granules easily visible in 5% to 10% of cells. Grade 2+ had a grossly blue color and granules were present in about 40% of cells. Grade 3+ included specimens with most cells heavily laden with large granules.

Results

Forty women were studied, and, as shown in Table I, 22 had hemoglobin SS disease, 16 had SC disease, and two had sickle–β-thalassemia. Prophylactic transfusions in most patients were begun by midpregnancy and a mean of 13.6 (range 3 to 28) red blood cell units per woman was given. Before the index pregnancy, 18 of the 40 women had been transfused on one or more occasions, and five had received >10 units. None of these women had clinically evident liver disease at the time of biopsy; however, five of 18 with SS disease and one of 15 with SC disease had a serum transaminase level that exceeded 100 U/L (normal, 5 to 35 U/L) at some time during pregnancy. The one complication from liver biopsy was a small intrahepatic hematoma that resolved spontaneously in a woman with hemoglobin SC disease.

Each histologic specimen was evaluated and graded by one of us (E. H. E.) experienced in liver histopathology and the findings are summarized in Table II. The lobular architecture (identifiable portal tracts and central veins in their normal configuration) of the liver was undisturbed in each of the biopsy specimens examined. Mild abnormalities of the sinusoidal architecture (single-cell-thick plates radially oriented about central veins) were noted in slightly more than half (28 to 40) of the biopsy specimens (Figs. 1A and 1B). Single-cell hepatocyte necrosis, although encountered in more than half the biopsy specimens, was widely scattered and rare in any one specimen, and widespread necrosis was not identified (Fig. 2). Mild to moderate hepatocellular regeneration was also a prominent feature in most of the specimens. Evidence of extramedullary hematopoiesis was observed frequently.

Table II. Selected microscopic findings in liver biopsy specimens from 40 women with sickle hemoglobinopathies

Finding	*Degree of abnormality*			
	0	*1+*	*2+*	*3+*
Hepatocytes				
Single-cell necrosis	15	25	—	—
Widespread necrosis	40	—	—	—
Regeneration	5	18	17	—
Iron	12	14	12	2
Portal tracts				
Fibrosis	23	16	1	—
Cirrhosis	40	—	—	—
Septa	40	—	—	—
Inflammation	25	15	—	—
Marginal disruption	29	11	—	—
Sinusoids				
Dilatation	7	13	14	6
Congestion	5	22	9	4
Erythrophagocytosis	1	39	—	—
Fibrosis	15	19	6	—
Erythrocyte sickling	17	9	13	1
Iron	7	20	10	3

Pathologic changes in the portal tracts were exceedingly uncommon. None of the 40 specimens showed evidence of cirrhosis or formation of fibrous septa, and in only one case was more than an insignificant increase in portal fibrosis noted. Widely scattered areas of acute or chronic inflammation were present in a minority of cases, and disruption of the limiting plate surrounding the portal areas was either focal or absent. No biopsy specimen showed evidence of acute or chronic hepatitis.

The hepatic sinusoids often showed changes but collectively did not represent significant liver injury. Sinusoidal dilatation was graded as marked (3+) in 6 of 40 specimens (Fig. 3), mild to moderate (1 to 2+) in 27 of 40, and absent in seven specimens. Congestion was severe (3+) in 4 of 40, moderate (1+ to 2+) in 31 of 40, and absent in only 6 of 40 biopsy specimens. Erythrophagocytosis by Kupffer cells was also a near-constant feature (Fig. 4). Of the red blood cells seen in the sinusoids, approximately half were sickled. Mild to

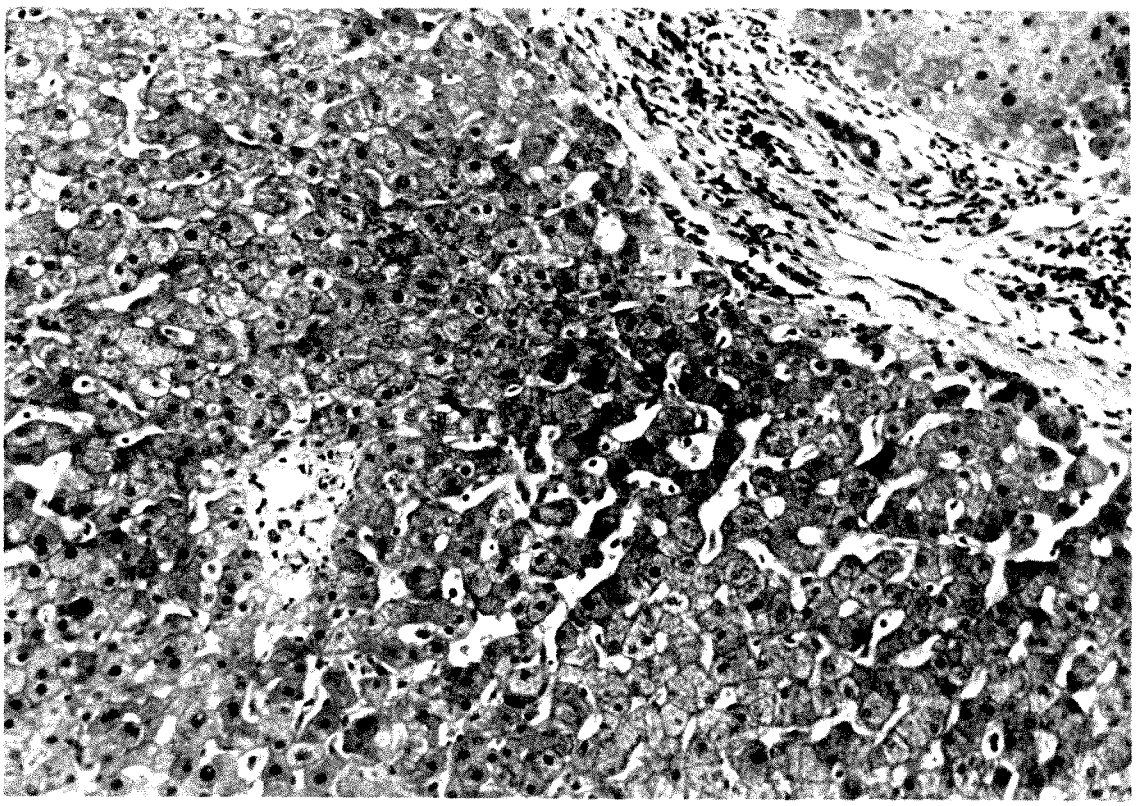


Fig. 1A. Portal tracts with intact limiting plates and single-cell-thick perioportal hepatocyte plates.

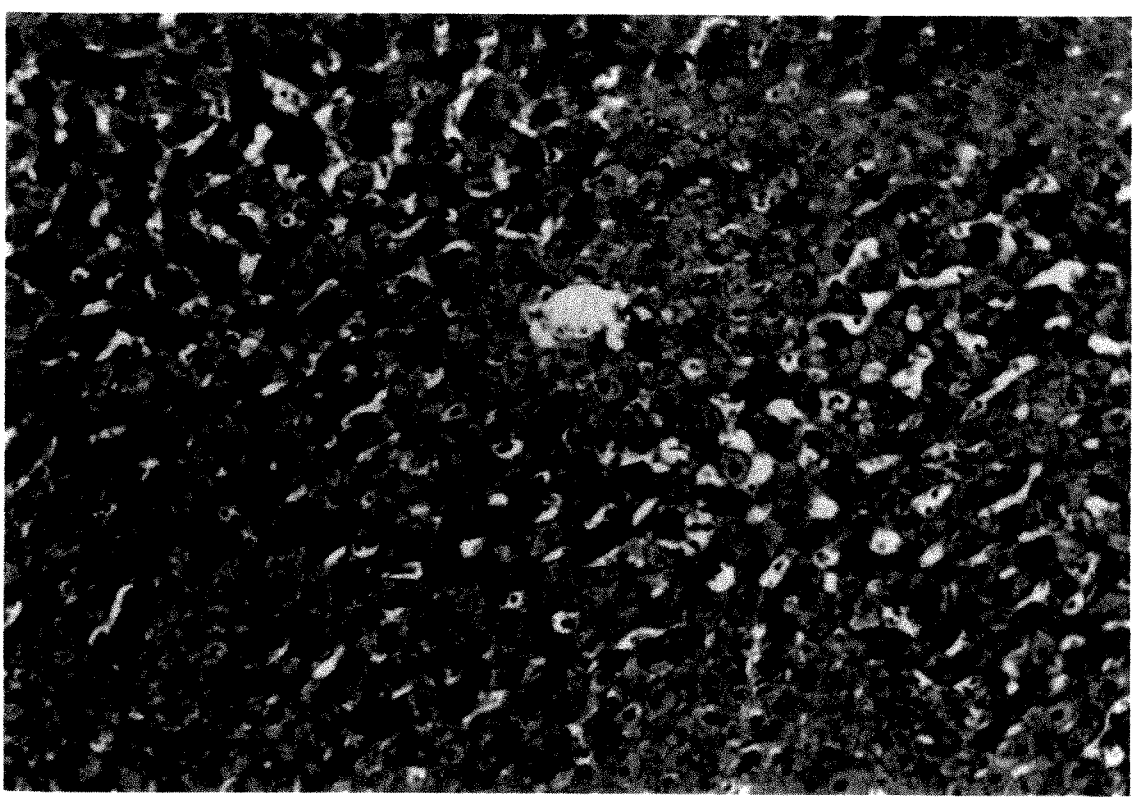


Fig. 1B. Centrilobular area showing central vein and sinusoidal dilatation without prominent congestion. Note single-cell-thick plates and absence of hypoxic injury (atrophy).

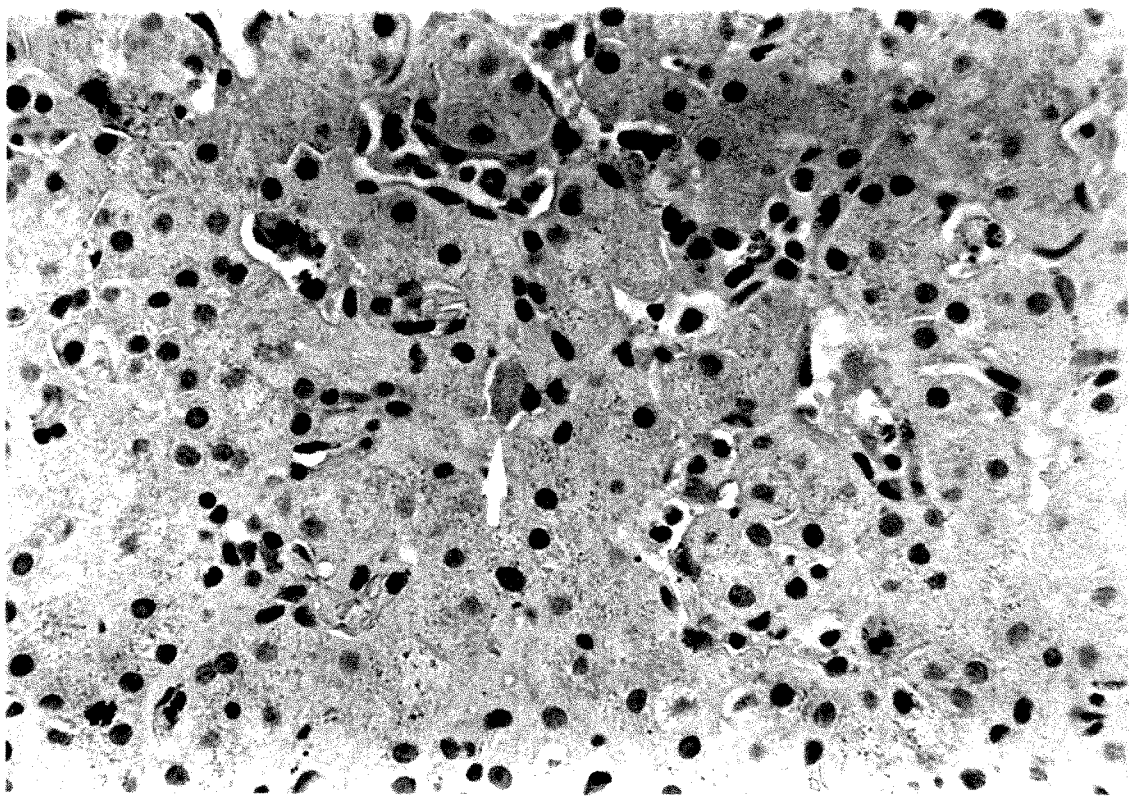


Fig. 2. Single-cell necrosis. *Arrow* indicates an acidophilic (Councilman-like) body.

moderate sinusoidal reticular fibrosis was present in slightly more than half the specimens.

Stainable iron was increased in each biopsy specimen. In a third of the specimens, iron deposition in hepatocytes exceeded that in Kupffer cells (Fig. 5), while the reverse was true in another third. The remaining third demonstrated nearly equal distribution of iron between the two sites. Only 2 of 40 specimens showed large granules of iron (3+) in most of the hepatocytes.

Comment

Schafer et al.[8] reported liver biopsy results from 10 of 15 adults with transfusion-dependent anemia who, over a 4-year period, were transfused with 80 to 210 (mean, 120) units of blood. They described "striking hemosiderosis" with iron deposition in both hepatocytes and Kupffer cells, and there was focal portal fibrosis and inflammation in the majority of cases. In contrast, the 40 pregnant women with sickle hemoglobinopathies described here were transfused prophylactically with an average of 13.6 units of red blood cells and none received more than 28 units. None of these asymptomatic women had evidence on liver biopsy of widespread necrosis, extensive inflammation, fibrous septa formation, or cirrhosis. Conversely, sinusoidal dilatation, erythrophagocytosis, and intrasinusoidal sickling usually were seen. Because normal pregnancy causes no definite changes in liver morphologic features, the histologic findings described here cannot be attributed to pregnancy. It seems likely that the difference in the number of units transfused and consequently in iron load is responsible for the minimal pathologic findings in our patients compared with those reported by Schafer et al.[8]

Histopathologic data derived from the liver biopsy specimens reported here represent the largest series of patients, pregnant or nonpregnant, in the literature to date and thus contribute significantly to the knowledge of liver involvement in sickle hemoglobinopathies. On the basis of 12 percutaneous liver biopsies, Rosenblate et al.[10] implied that all patients with sickle cell disease had similar hepatic abnormality and showed widely dilated and congested sinusoids, erythrophagocytosis by Kupffer cells, and parenchymal atrophy in the centrilobular regions. These changes were relatively minimal and amenable to regeneration without chronic destructive changes and were thought to be related to so-called sickle cell crises. Rosenblate et al.[10] confirmed the findings of earlier studies, which suggested that sinusoidal obstruction that was secondary to engorged Kupffer cells and sickled erythrocytes led to anoxia distal to the obstruction. Our patients usually did not have sickling episodes because they were given prophylactic transfusions, yet they showed similar histologic features with

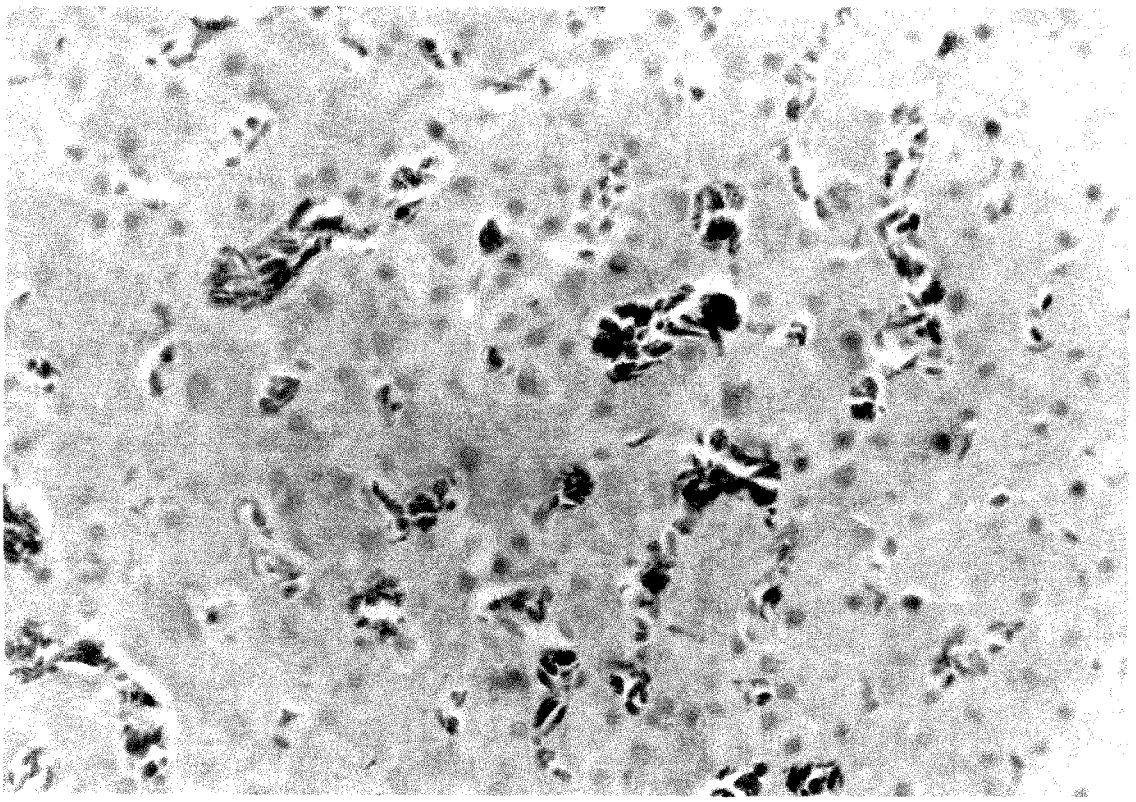


Fig. 3. Sinusoidal dilatation and congestion. Although the process is marked in this photomicrograph, there is no evidence of anoxic damage. Note the number of sickled erythrocytes.

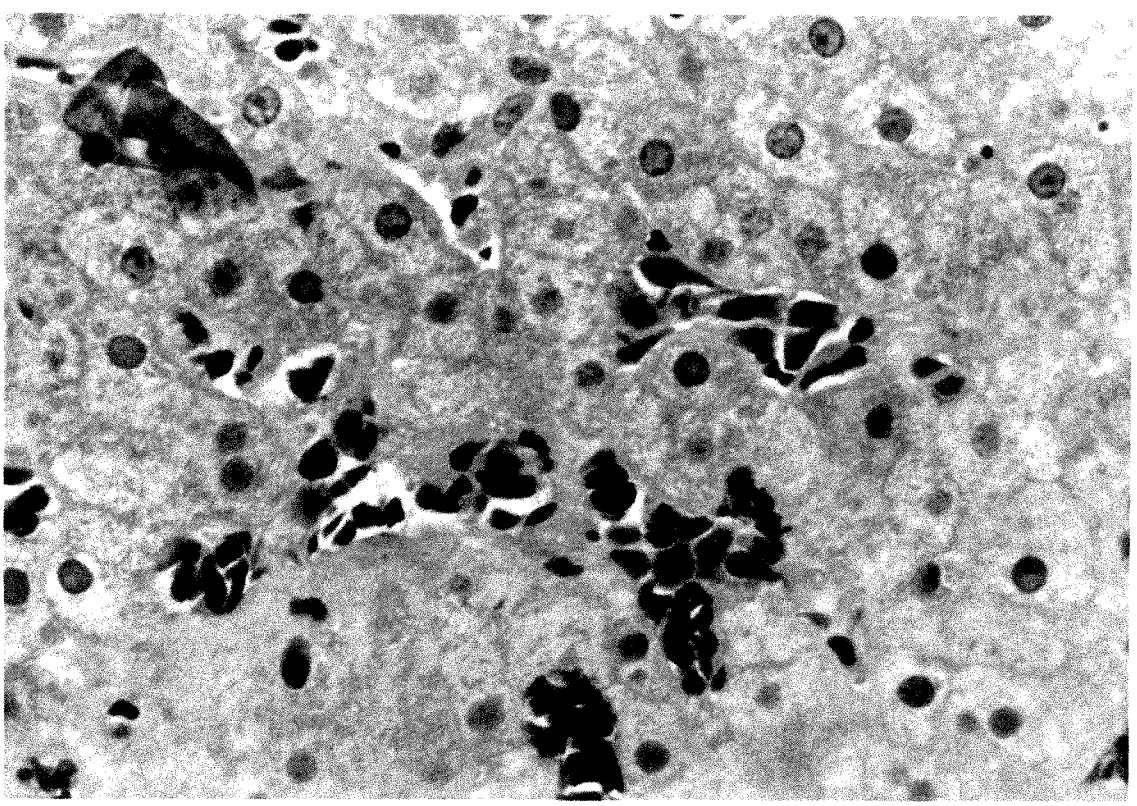


Fig. 4. Erythrophagocytosis. Shown are Kupffer cells with ingested erythrocytes.

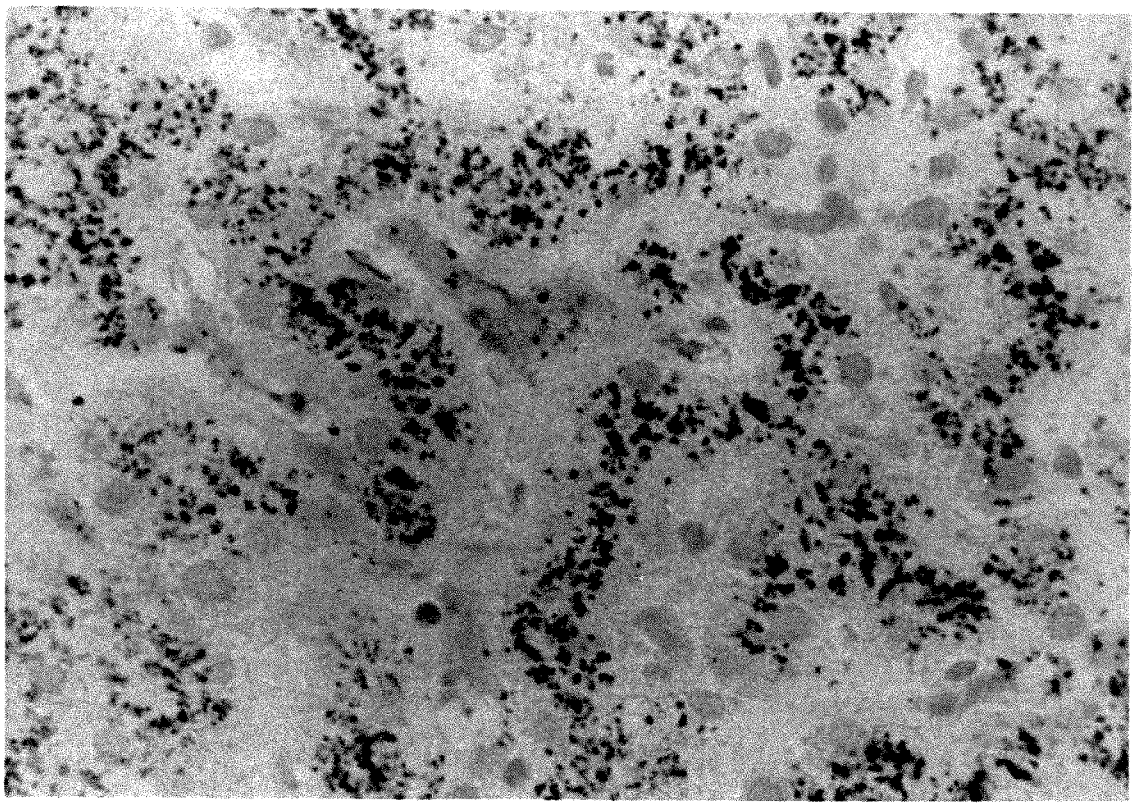


Fig. 5. Prussian blue stain for iron. The iron is predominantly present in the hepatocytes and is seen as darkly staining granules.

the exception that centrilobular atrophy was not observed.

There is evidence that other, more significant pathologic findings in sickle cell patients usually are caused by superimposed illnesses. In an autopsy study spanning more than 90 years, Bauer et al.[11] concluded that the spectrum of otherwise unexplained liver injury in patients with sickle cell disease most likely resulted from sinusoidal obstruction and anoxia. However, 44 of their 70 patients had liver disease attributed to a variety of complicating illnesses, including viral hepatitis, sepsis, shock, toxin exposure, hemochromatosis, and cardiac cirrhosis. Johnson et al.[12] performed liver biopsies in 11 patients with sickle cell disease who had persistently abnormal liver function tests and concluded that all had other complicating illnesses. This group[13] later compared histologic findings from 19 liver biopsy specimens with 32 autopsy specimens and found ischemic necrosis almost exclusively in the postmortem material. They noted intrasinusoidal sickling and Kupffer cell erythrophagocytosis in almost all specimens but found no correlation between these histologic changes and the degree of transaminase elevation. Additionally, although perivenular necrosis would be expected if sinusoidal obstruction led to hypoxic or anoxic liver injury, it was notably absent.

Importantly, Omata et al.[13] performed incidental intraoperative liver biopsy in five patients at the time of cholecystectomy and found no significant morphologic changes other than intrasinusoidal sickling and Kupffer cell erythrophagocytosis. This small group of control patients most closely approximates the 40 otherwise asymptomatic women described here. Finally, Mills et al.[14] reported findings from 13 liver biopsies performed in patients with sickle cell disease and confirmed that sickled red blood cells, sinusoidal distention, and Kupffer cell erythrophagocytosis were found in all to some degree but did not correlate with evidence of hepatocellular damage or with clinical features.

We conclude, at least for a single pregnancy, that prophylactic erythrocyte transfusions do not lead to irreversible hepatic damage. Reversible changes in liver histologic characteristics did not correlate with the number of units transfused. Even though there was evidence of hepatic iron overload with stainable iron present to some degree in every biopsy specimen, the associated histopathologic changes were no more than those previously reported in patients with sickle cell disease. Unfortunately, we cannot exclude longer-term adverse effects of prophylactic transfusions, for example, chronic hepatitis or other infectious complications. Because of this, we continue to advocate lim-

iting the use of transfusion therapy to a single pregnancy.

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Comparison of a rapid enzyme-linked immunosorbent assay test and the Gram stain for detection of group B streptococcus in high-risk antepartum patients

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Early-onset neonatal sepsis with group B streptococci is a major problem in the management of high-risk obstetrics. Intrapartum treatment of the colonized mother reduces neonatal acquisition; however, many high-risk patients are delivered before culture results are available. This study prospectively evaluated a new enzyme-linked immunosorbent assay and the Gram stain for their accuracy in rapid detection of group B streptococci in 131 high-risk patients. Twenty positive cultures for group B streptococci were identified in the study population and were used as the control for test comparisons. The enzyme-linked immunosorbent assay test was 60% sensitive, whereas the Gram stain was 45% sensitive. The enzyme-linked immunosorbent assay showed an increase in sensitivity as the colony count increased; however, two cases of severe neonatal sepsis occurred in patients with low colony counts and both had enzyme-linked immunosorbent assay negative results. In conclusion, the need for a rapid sensitive test for group B streptococci detection still exists. (Am J Obstet Gynecol 1990;163:965-7.)

Key words: Group B streptococci, ELISA, Gram stain, sensitivity

Group B streptococci are the leading cause of neonatal sepsis with 12,000 to 15,000 cases reported each year.[1] Early-onset infection usually occurs within the first 24 hours of life and can lead to pneumonia, septicemia, meningitis, septic shock, and in some cases death.[1] The transmission of group B streptococci to the infant with early-onset disease is thought to result from intraamniotic infection or with passage through the birth canal.[2] It has been shown that if the mother is treated with antibiotics before delivery neonatal outcome is improved by apparent ablation of vertical transmission.[3, 4]

Group B streptococcal colonization ranges from 5% to 30% of all pregnant women.[5] Attempts to obtain cultures from all pregnant women, with treatment of those with positive results has not been cost effective and recolonization is common.[6, 7] In addition, 80% of serious group B streptococcal infections occur in the premature infant.[8, 9] Therefore attention has focused primarily on obtaining cultures from high-risk patients with treatment before delivery if possible.[10] Unfortunately, many of these high-risk patients are delivered before culture results are available.

The purpose of this study was to prospectively evaluate a new rapid enzyme-linked immunosorbent assay (ELISA) test (Equate, marketed by Binax, South Portland, Me.) and the Gram stain to determine if either test was sensitive enough to use in the management of these high-risk patients.

Material and methods

All patients for the study were prospectively identified from Jan. 1, 1989, to July 30, 1989, at Memorial Womens Hospital of Long Beach. In every patient three swab samplings were obtained. The sampling technique was the same for each swab and from patient to patient. This technique would start at the cervix and then sweep the vaginal walls and introitus on removal in an attempt to sample the entire birth canal. Each case had three tests performed: the ELISA test, a Gram stain, and a culture for group B streptococci on selective medium; a separate swab was used for each test. The culture results were used as the prevalence rate to which the two rapid tests were compared. All three tests were performed as they were received by the laboratory; batching of tests did not occur.

The culture was performed with a three-quadrant technique. The swab was applied to the first quadrant and then a wire loop was passed through this quadrant to inoculate the second and third quadrants. Culture results were reported as light growth if growth

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Table I. Comparison of ELISA and Gram stain results with the 20 positive group B streptococcal cultures

Rapid test	*True-positive*	*False-positive*	*True-negative*	*False-negative*	*Total*
ELISA	12	9	102	8	131
Gram stain	9	41	70	11	131

Table II. Effectiveness of ELISA and Gram stain in identifying group B streptococci

Evaluation	*ELISA*	*Gram stain*	*Significance*
Sensitivity (%)	60	45	NS
Specificity (%)	92	63	$p < 0.00001$
Positive predictive value (%)	57	18	$p < 0.003$
Negative predictive value (%)	93	86	NS

Table III. Comparison of ELISA and Gram stain results with amount of group B streptococcal growth in culture

Culture growth	*No. of cases with group B streptococci*	*No. of positive ELISA results*	*No. of positive Gram stains*
Light	9	4 (44%)	4 (44%)
Moderate	6	4 (67%)	3 (50%)
Heavy	5	4 (80%)	2 (40%)
TOTAL	20	12	9

Light growth = colony count <10,000 cfu; moderate growth = colony count 10,000 to 100,000 cfu; heavy growth = colony count >100,000 cfu.

was confined to the first quadrant (colony count <10,000 cfu). Heavy growth was reported if growth reached the third quadrant (colony count >100,000 cfu) and moderate growth was reported if growth occurred in the first and second quadrants only (colony count 10,000 to 100,000 cfu).

The ELISA test was performed as described in the manufacturer's instructions. A positive and negative control was run with each test sample. A critical part of the test is the washing step that requires at least five forceful washings of the test tube with free-running tap water. Additional washings were acceptable and each test case had from five to eight washes performed. A positive test for group B streptococci results in a distinct blue color whereas a negative test is colorless. The results of the ELISA test were blinded from the clinician until completion of the entire study.

The ELISA test instructions state that the reliability of the test can be seen for up to 2 weeks after collection. Therefore a few swabs were saved and were retested at 7 and 14 days. The results of these repeat tests were compared with the initial test results.

The Gram stain was performed in the usual fashion and the presence of any gram-positive cocci indicated a positive result.

Results

One hundred thirty-one high-risk patients were evaluated. The mean gestational age was 30.4 weeks (range, 22 to 40 weeks). Five cases were ≥36 weeks of gestation and had prolonged premature rupture of membranes with no prenatal care. The remaining 126 cases were ≤35 weeks' gestation with either preterm premature rupture of the membranes (80 cases), premature labor (37 cases), or premature cervical dilatation (9 cases). None of the 131 patients received antibiotics before swabs for the study were obtained.

There were 20 cases with a positive group B streptococcal culture result, an incidence of 15%. The results of the ELISA and Gram stain in comparison with these 20 positive culture cases are seen in Table I. The sensitivity, specificity, and positive and negative predictive values of each rapid test are seen in Table II. Neither test was highly sensitive in identifying group B streptococcal colonization. However, the ELISA was statistically more specific and had a better positive predictive value.

In evaluation of each rapid test in regard to sensitivity with relation to the colony count (Table III), it was found that the sensitivity of the ELISA increased as the colony count increased. The sensitivity of the Gram stain did not change as the colony count increased.

Sixty patients (46%) were delivered of their infants <24 hours after admission and before culture results were available. Eight of these 60 patients (40% of the positive group B streptococcal cultures) were colonized with group B streptococci. The ELISA and the Gram stain were each positive for group B streptococci in five of these eight cases. Therefore 37% of group B streptococci–positive patients who were delivered before culture results were known would have been missed if treatment was based only on these rapid tests.

The ELISA test kit requires the use of a dry swab. The majority of microbiologic tests, however, use a wet swab. Eighty-five cases had both a wet and a dry swab run simultaneously and the results were the same in every case. In addition, six cases had repeat tests run 7 to 14 days after the initial test. Three cases were positive for group B streptococci and three were neg-

ative. The results of the repeat tests were identical to the initial test result in every case.

All 131 cases were evaluated through delivery. The 12 patients with positive group B streptococcal cultures who were not delivered within 24 hours were all treated with antibiotics and no group B streptococcal infections occurred. There were no cases of group B streptococcal infection in the 111 cases with negative culture results. Of the eight patients with positive group B streptococcal cultures who were delivered within 24 hours, four were treated before delivery because of maternal fever and no group B streptococcal infections occurred. The remaining four patients did not receive treatment, and in two of these infants group B streptococcal sepsis developed and the infants ultimately died. One of these was a 26-week gestation with extreme prematurity as a factor; the other was a 32-week gestation. The culture revealed light growth of group B streptococci in both cases.

Comment

We evaluated the new Equate ELISA test for its ability to identify group B streptococci colonization in high-risk pregnant patients. Unfortunately, the test was only 60% sensitive. If the only concerns were for patients with moderate or heavy growth by culture, the sensitivity for the ELISA increased. However, 20% to 33% of patients with positive group B streptococcal cultures would still have been undetected. In addition, the two infants with documented group B streptococcal sepsis occurred in cases with light growth by culture when both the ELISA and the Gram stain were negative.

The results of the Gram stain were no different. If treatment was isolated to only those patients with a positive Gram stain, up to 50% of patients with group B streptococci would have been undetected and a large number of patients would have received treatment when it was not needed. As seen in our data, the Gram stain yields a large number of false-positive results. This is most likely because of the numerous other gram-positive organisms that can be found in the female genital tract other than group B streptococci. We have no explanation for the significant number of false-positive ELISA results that were obtained.

When the study was first initiated, the senior medical technician (W. W. F.) performed the ELISA test. The sensitivity of the test for identifying group B streptococci in her hands was 75%. As the study progressed, other medical technicians were allowed to perform the test (as would occur in the everyday setting) and the sensitivity dropped to only 43%.

The ELISA test kit requires the use of a dry swab; however, the use of a wet swab did not alter the results in this study. In addition, it appears that the accuracy of the test does remain stable for up to 7 to 14 days after its collection as stated in the product information package.

Because many patients with positive group B streptococcal test results are delivered before culture results are available, the need still exists for a rapid sensitive test. One management option is to treat all high-risk patients until the culture results are known. However, this would result in the treatment of many patients in whom treatment might not be indicated, possibly resulting in the development of resistant organisms. We agree with the treatment plan of Minkoff and Mead,[11] which proposes antibiotic therapy only for high-risk patients if delivery is inevitable before culture results are known. This proposal avoids unnecessary treatment of stable patients when time allows for the culture results but at the same time treats all patients who are colonized with group B streptococci but who deliver too quickly. We do not recommend the use of these rapid tests as the only basis for treatment in high-risk patients because of their poor sensitivity. Therefore the evalution of rapid tests for group B streptococcal detection should continue until a sensitive test is ultimately produced.

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Amniotic fluid glucose concentration: A rapid and simple method for the detection of intraamniotic infection in preterm labor

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The purpose of this study was to determine whether amniotic fluid glucose concentrations is of value in the rapid diagnosis of intraamniotic infection. Amniocenteses were performed in 168 patients with preterm labor and intact membranes. Amniotic fluid was cultured for aerobic and anaerobic bacteria, as well as *Mycoplasma* species. The prevalence of positive amniotic fluid cultures was 13.6% (23/168). Patients with positive amniotic fluid cultures for microorganisms had significantly lower median amniotic fluid glucose concentrations than patients with negative amniotic fluid cultures (median 11 mg/dl, range 2 to 30 mg/dl vs median 28 mg/dl, range 3 to 74, respectively; $p < 0.001$). Amniotic fluid glucose concentrations below 14 mg/dl had a sensitivity of 86.9% (20/23), a specificity of 91.7% (133/145), a positive predictive value of 62.5% (20/32), and a negative predictive value of 97.8% (133/136) in the detection of a positive amniotic fluid culture. Amniotic fluid glucose determination is a rapid, sensitive, inexpensive, and simple test for the detection of intraamniotic infection in women with preterm labor and intact membranes. (AM J OBSTET GYNECOL 1990;163:968-74.)

Key words: Glucose, intraamniotic infection, chorioamnionitis, preterm labor, prematurity, Gram stain, amniotic fluid

Strong evidence supports an association of intraamniotic infection with preterm labor and delivery.[1] Patients in preterm labor with intact membranes and positive amniotic fluid cultures are more likely to have clinical chorioamnionitis and fail to respond to tocolysis.[1, 2] Furthermore, neonates born to women with positive amniotic fluid cultures are at an increased risk for infectious complications.[2]

The early diagnosis of intraamniotic infection is a desirable clinical goal. However, clinical signs of infection are insensitive and will detect only 12% of patients with positive amniotic fluid cultures in women with preterm labor and intact membranes.[2] While amniotic fluid cultures are widely used to assess the microbiologic state of the amniotic cavity, results are not immediately available and may take up to 5 days. Rapid methods for the detection of infection, such as the Gram stain and the acridine orange stain of amniotic fluid, are insensitive, detecting only 50% to 60% of all intraamniotic infections.[3, 4] Other tests, such as gas-liquid chromatographic analysis of organic acids in amniotic fluid, require expensive equipment and trained personnel and are not available in most medical centers. Thus there is a need for a sensitive, simple, and rapid test for the detection of intraamniotic infection.

A decreased glucose concentration in several body fluids (i.e., cerebrospinal fluid, pleural fluid, and synovial fluid) has been used for the diagnosis of infection.[5-7] The purpose of this study was to determine whether amniotic fluid glucose concentration could be of value in the diagnosis of intraamniotic infection. The value of amniotic fluid glucose concentration in the diagnosis of intraamniotic infection was first suggested by Dr. Brian Kirshon (personal communication, 1989).

Material and methods

Patient population. The study population consisted of 168 consecutive patients who were admitted to Yale–New Haven Hospital with the diagnosis of preterm labor and intact membranes from March 3, 1988, to May 26, 1989, and who underwent amniocenteses for evaluation of the microbiologic status of the amniotic fluid. Patients with known abnormal glucose tolerance test results or with overt diabetes mellitus were excluded. Preterm labor was defined as the presence of

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regular uterine contractions with a frequency of at least two every 10 minutes. Rupture of membranes was excluded by testing for pooling, Nitrazine paper reaction, and ferning. Ritodrine, terbutaline, or magnesium sulfate was administered intravenously for tocolysis after amniocentesis. Failure of tocolysis was diagnosed when cervical dilatation progressed beyond 5 cm or delivery occurred.

Retrieval of amniotic fluid. In all cases amniotic fluid was retrieved by transabdominal amniocentesis, which was performed under ultrasonographic guidance.

Microbiologic culture technique. Amniotic fluid was transported to the laboratory in a capped plastic syringe immediately after collection. These conditions precluded air contact with the specimen. Plating occurred within 30 minutes of collection in all cases. Amniotic fluid was cultured for aerobic and anaerobic bacteria, as well as for *Mycoplasma* species (*Mycoplasma hominis* and *Ureaplasma urealyticum*), according to methods previously described.[4]

Gram stain examination. Gram stain examinations were performed by using commercial reagents (crystal violet, saffranin, and Gram's iodine [Difco Laboratories, Detroit]) under standard conditions. Stained slides were then examined by trained technologists, and the presence or absence of microorganisms was noted. The results of the Gram stain examinations were shared with the clinicians. Patients with negative Gram stain examinations for bacteria were given tocolysis. Patients with positive Gram stain examination of amniotic fluid for bacteria were given parenteral antibiotics and allowed to labor. A positive Gram stain for bacteria was an indication for discontinuing tocolysis.

Amniotic fluid glucose determinations. Amniotic fluid was centrifuged at 700 *g* for 10 minutes at 4° C and stored at −70° C until assayed. Glucose analysis was performed by the glucose oxidase method with a Beckman glucose analyzer. Samples were run in duplicate. Results were not available for patient management. The coefficient of variation was 5%.

Criteria for diagnosis of chorioamnionitis and neonatal sepsis. Intraamniotic infection was defined as the presence of a positive amniotic fluid culture.[1] Clinical chorioamnionitis was defined according to the criteria proposed by Gibbs et al.[8] Neonatal sepsis was diagnosed by the presence of a positive culture of blood, urine, or cerebrospinal fluid.

Statistical analysis. A Mann-Whitney test was used to compare amniotic fluid glucose concentrations between infected and noninfected patients. A receiver operator characteristic curve analysis was conducted with the program True Epistat (Epistat Services, Richardson, Tex.). Diagnostic indices (sensitivity, specificity, and positive and negative predictive values) for the detection of a positive amniotic fluid culture were calculated for both the Gram stain and amniotic fluid glucose.

Results

The criteria for inclusion into this study were met by 168 patients, 54.1% (91/168) of whom went on to have a preterm delivery. The remainder were delivered at term. The prevalence of positive amniotic fluid cultures was 13.6% (23/168).

Fig. 1 displays amniotic fluid glucose concentrations according to culture results. Patients with positive amniotic fluid cultures for microorganisms had significantly lower median amniotic fluid glucose concentrations than patients with negative amniotic fluid cultures (median 11 mg/dl, range 2 to 30 mg/dl vs median 28 mg/dl, range 3 to 74, respectively; $p < 0.001$, Mann-Whitney test).

To describe the relationship between the sensitivity (true-positive rate) and the false-positive rate for different values of amniotic fluid glucose in the detection of a positive amniotic fluid culture, a receiver operator characteristic curve was constructed. Fig. 2 displays the receiver operator characteristic curve (area under the curve 0.93; SE 0.03; z 14.1; $p < 0.001$). The curve is well above the 45-degree line, indicating that an abnormal test result (reduced amniotic fluid glucose concentration) increases the probability of a positive amniotic fluid culture. As with any other diagnostic test, there is a trade-off between the sensitivity (true-positive rate) and the false-positive rate (100 − Specificity). We chose to present the diagnostic indices using a cutoff at 14 mg/dl, as this value seems to represent a reasonable compromise between a true-positive and a false-positive rate.

A glucose level below 14 mg/dl had a sensitivity of 86.9% (20/23), a specificity of 91.7% (133/145), a positive predictive value of 62.5% (20/32), and a negative predictive value of 97.8% (133/136). On the other hand, the diagnostic indices for the Gram stain examination of amniotic fluid were: sensitivity of 65.2% (15/23), specificity of 99.3% (144/145), positive predictive value of 93.7% (15/16), and negative predictive value of 94.7% (144/152).

When the Gram stain and glucose level (below 14 mg/dl) were used in combination (either test result considered abnormal), the diagnostic indices were sensitivity of 86.9% (20/23), specificity of 91% (132/145), positive predictive value of 60.6% (20/33), and negative predictive value of 97.8% (132/135).

There were 131 patients with negative Gram stains and glucose concentrations above 14 mg/dl. Three had positive amniotic fluid cultures (two with *Ureaplasma urealyticum* and one with *Gardnerella vaginalis*). All three patients failed to respond to intravenous tocolysis and were delivered of preterm neonates.

Table I displays the clinical data of the 12 patients with amniotic fluid glucose concentrations of <14 mg/dl and negative amniotic fluid cultures for bacteria and *Mycoplasma* species. Although all of these patients

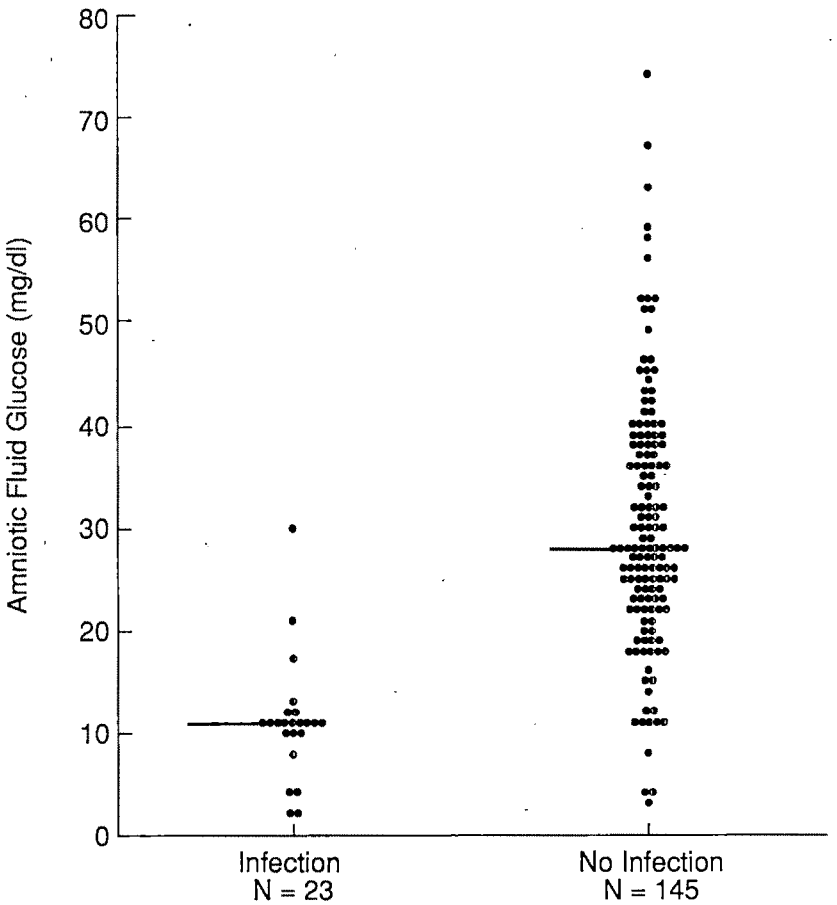


Fig. 1. Amniotic fluid glucose concentrations in the study population. The median amniotic fluid glucose concentration in patients with intraamniotic infection was significantly lower than in patients with negative amniotic fluid cultures (median 11 mg/dl, range 2 to 30 mg/dl vs median 28 mg/dl, range 3 to 74, respectively; $p < 0.0001$).

received parenteral tocolysis, 75% (9/12) went on to have a preterm delivery. Five of the nine patients with negative amniotic fluid cultures had been treated with antibiotics before undergoing amniocentesis, and one of the neonates subsequently had documented neonatal sepsis. In addition, one neonate was diagnosed to have congenital syphilis, but treponemas were not recovered from the amniotic fluid. Two of the three remaining patients had no clinical evidence of infection (maternal or neonatal), but their placentas showed acute inflammatory lesions (histopathologic chorioamnionitis).

Three patients with low glucose concentrations and negative amniotic fluid cultures were delivered at term. One patient had polyhydramnios of an unknown cause. The second patient had fever (101° F) and was treated with erythromycin because of a positive endocervical culture for *Chlamydia trachomatis*. The remaining patient had no evidence of an infectious process.

Table II displays the clinical course and microbiologic characteristics of patients with positive amniotic fluid cultures. Twenty-one percent (5/23) of patients had polymicrobial infections. Eight patients had negative Gram stains for microorganisms, and five of these had glucose concentrations below 14 mg/dl.

Clinical chorioamnionitis occurred in 2.4% (4/168) of patients. Three patients had positive amniotic fluid cultures for microorganisms and amniotic fluid glucose concentrations below 14 mg/dl, while the remaining patient had a negative culture of the amniotic fluid. This woman had lower abdominal pain, a temperature of 106° F, and leukocytosis (a white blood cell count of 22,300/mm^3) and underwent a cesarean section because of fetal distress. Placental examination did not show any evidence of inflammation, and the newborn had no evidence of sepsis. The amniotic fluid glucose concentration was 28 mg/dl.

The only neonate with sepsis was born to a woman with a positive amniotic fluid culture. The amniotic fluid glucose concentration in this case was 12 mg/dl.

Of the 168 patients included in the study, 149 received a trial of tocolysis (15 patients had a positive Gram stain, and four additional patients had tocolysis discontinued because of maternal or fetal indications). A low glucose concentration (<14 mg/dl) had a

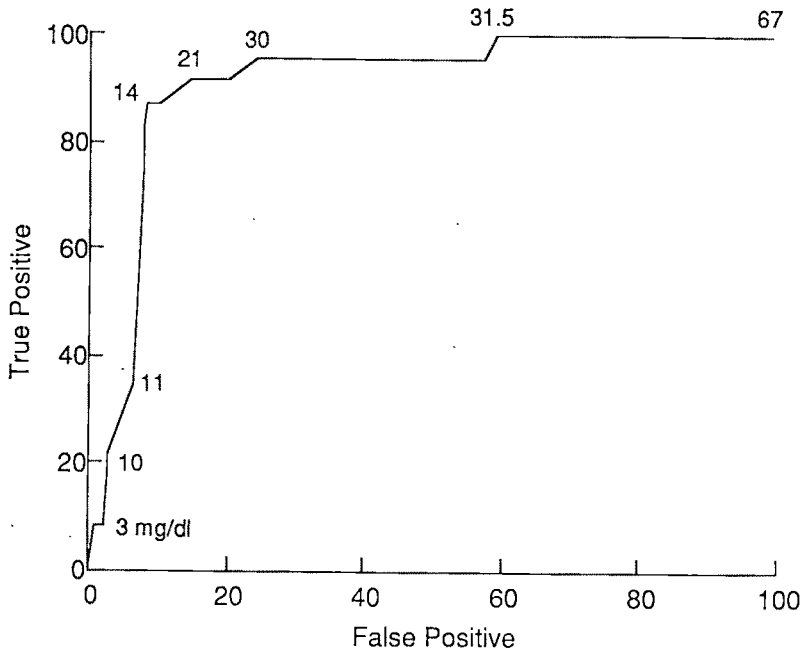


Fig. 2. A receiver operator characteristic curve analysis of the value of the amniotic fluid glucose concentration in diagnosis of a positive amniotic fluid culture (area under the curve 0.93, SE 0.03; z 14.1; $p < 0.001$). The numbers in the figure represent amniotic fluid glucose concentrations in milligrams per deciliter.

sensitivity of 37.9% (11/29), a specificity of 88.3% (106/120), a positive predictive value of 44% (11/25), and a negative predictive value of 85.4% (106/124) for the prediction of failure to respond to tocolytic therapy.

Comment

The data clearly demonstrate that microbial invasion of the amniotic cavity in women with preterm labor with intact membranes is associated with reduced glucose concentration in amniotic fluid (Fig. 1). Similar observations have been made in other body fluids (i.e., cerebrospinal fluid) in the setting of bacterial infection.[5-7]

Why is microbial invasion of the amniotic cavity associated with a reduced glucose concentration? In cerebrospinal fluid, three mechanisms have been invoked to explain a similar phenomenon: (1) metabolism of glucose by microorganisms, (2) consumption of glucose by activated neutrophils, and (3) changes in glucose transport across the hematoencephalic barrier. The most likely explanation for the low glucose concentration in cerebrospinal fluid is metabolism of glucose by white blood cells and bacteria. The evidence suggesting that glucose catabolism by activated neutrophils is the primary mechanism involved includes the following: (1) Neutrophils obtained from septic cerebrospinal fluid consume glucose at a rate that is two to three times higher than that of neutrophils from noninfected patients[10]; (2) incubation of cerebrospinal fluid with a combination of leukocytes and bacteria results in a lowered glucose concentration, while incubation by either one alone does not have the same effect[11]; (3) irradiated leukopenic dogs do not respond to pneumococcal meningitis with pleocytosis or with a reduction in cerebrospinal fluid glucose.[12] In contrast to bacterial infections, viral infections are not associated with a reduction in glucose concentrations. In viral infections the mononuclear cells are predominant. These cells are known to consume glucose at a lesser rate than neutrophils. An important question that remains to be answered is whether these aforementioned mechanisms are operative in amniotic fluid. The observation that six women who had negative amniotic fluid cultures for microorganisms and who also had acute inflammatory lesions of the placenta (see Table I) had reduced amniotic fluid glucose concentrations indicates that this finding could occur in the absence of viable microorganisms. Therefore, an inflammatory host response is probably associated with reduced glucose concentration in amniotic fluid.

In our study amniotic fluid glucose determinations, with a cutoff ≤14 mg/dl, had a sensitivity of 86.9% in the detection of intraamniotic infection while the sensitivity of the Gram stain was 65.2%. This difference fell short of reaching statistical significance with our sample size (23 patients with intraamniotic infections). The false-positive rate (100 − Specificity) of the Gram stain was lower than that of the amniotic fluid glucose concentration (0.7% vs 8.3%; $p < 0.05$). However, the

Table I. Clinical information and amniotic fluid concentrations in patients with false-positive results

Patient No.	*Amniotic fluid glucose concentration (mg/dl)*	*Gestational age at amniocentesis (wk)*	*Gestational age at delivery (wk)*	*Tocolysis response*	*Antibiotics before amniocentesis*	*Histologic chorioamnionitis**	*Comments*
1	3	33	33	No	No	Yes	
2	4	29	29	No	Yes	Yes	Neonate with congenital syphilis
3	4	34	35	No	Yes	N/A	Maternal fever
4	8	33.5	39	Yes	Yes	N/A	*Chlamydia trachomatis* endocervicitis
5	11	31	32	No	No	Yes	
6	11	25	25	No	Yes	Yes	Neonatal sepsis
7	11	34	40	Yes	No	N/A	
8	11	27	27	No	Yes	Yes	Neonatal viral meningitis
9	11	30	30	No	No	No	Foul-smelling amniotic fluid at delivery
10	12	33	33	No	No	Yes	
11	12	34	37	Yes	No	N/A	Massive polyhydramnios
12	14	35	35	No	Yes	N/A	Urinary tract infection

**N/A*, Placental histologic data were not available.

Table II. Clinical data, Gram stain, and amniotic fluid concentrations in patients with positive amniotic fluid cultures

Patient No.	*Gestational age at amniocentesis (wk)*	*Amniotic fluid glucose concentration (mg/dl)*	*Gram stain**	*Culture*	*Colony count (CFU/mm³)*	*Clinical chorioamnionitis*
1	25	2	+	*Candida tropicalis*	30,000	No
2	25	2	+	Mixed aerobic flora of 3 varieties	—	No
3	28.5	4	+	*Fusobacterium nucleatum*	>100,000	Yes
4	32	4	+	*Mycoplasma hominis*	—	Yes
				Ureaplasma urealyticum	—	
				Haemophilus influenzae	>100,000	
5	26	8	+	*Capnocytophaga* species	>100,000	Yes
				Clostridium species	>100,000	
6	24	10	+	Mixed anaerobic flora	>100,000	No
				Mycoplasma hominis	—	
7	25.5	10	+	*Streptococcus agalactiae*	>100,000	No
8	29	10	−	*Ureaplasma urealyticum*	—	No
9	23	11	+	*Fusobacterium nucleatum*	>100,000	No
10	23	11	+	*Gardnerella vaginalis*	50,000	No
11	24	11	+	*Streptococcus agalactiae*	>100,000	No
12	25	11	+	*Fusobacterium nucleatum*	1,000 cfu	No
13	28.5	11	−	*Ureaplasma urealyticum*	—	No
14	29	11	+	*Gardnerella vaginalis*	>100,000	No
15	29.5	11	−	*Staphylococcus aureus*	—	No
16	31	11	−	*Ureaplasma urealyticum*	—	No
17	33	11	−	*Fusobacterium* species	20,000	No
18	23	12	+	*Mycoplasma hominis*	—	No
19	24	12	+	*Gardnerella vaginalis*	>100,000	No
				Peptostreptococcus species	1,000	
20	34	13	+	*Peptostreptococcus* species	>100,000	No
21	31.5	17	−	*Ureaplasma urealyticum*	—	No
22	24	21	−	*Ureaplasma urealyticum*	—	No
23	34	30	−	*Gardnerella vaginalis*	>100,000	No

*All patients with positive Gram stains received antibiotics.

false-positive rate of amniotic fluid glucose concentration deserves comment. Seventy-five percent (9/12) of patients with low amniotic fluid glucose concentrations went on to deliver a preterm neonate despite intravenous tocolysis. Six of the seven placentas examined from women delivered prematurely had histologic evidence of chorioamnionitis. Thus an infectious process that was not detected by microbiologic examinations of

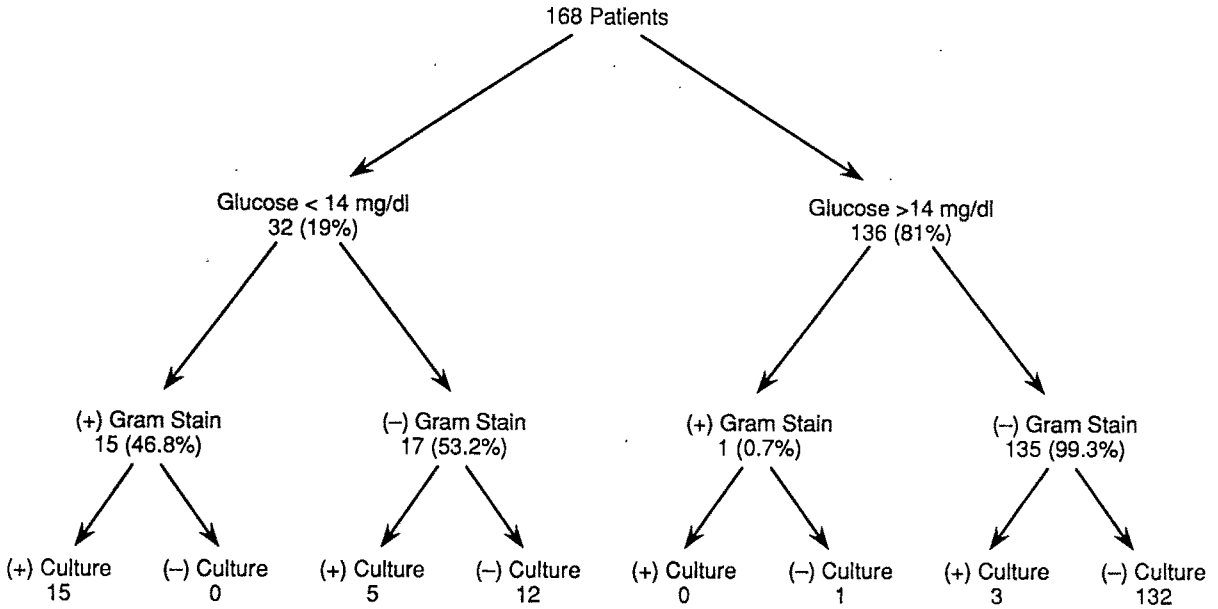


Fig. 3. Flow diagram of the results of amniotic fluid glucose determination, Gram stain, and culture of amniotic fluid.

amniotic fluid might have been responsible for the acute inflammatory lesions in the placenta.

The failure to recover microorganisms may have resulted from either antibiotic administration before amniocentesis (in five cases) or failure of growth of fastidious microorganisms. The possiblity exists that all nine patients with low amniotic fluid glucose concentrations and negative amniotic fluid cultures had an infectious process that escaped detection with current microbiologic techniques used in our laboratory.

There were three patients with low amniotic fluid glucose concentrations (8, 11, and 12 mg/dl, respectively) who were delivered at term. Two patients had clinical conditions that might explain the low concentration of glucose in amniotic fluid. The first patient had polyhydramnios, and this may have had a dilutional effect on amniotic fluid glucose concentration. The second patient had *Chlamydia trachomatis* endocervicitis and received antibiotics before amniocentesis. Antimicrobial therapy may have precluded successful isolation of a pathogen from amniotic fluid. We could not find any explanation for the reduced amniotic fluid glucose concentration observed in the third patient.

Despite the high sensitivity of amniotic fluid glucose determinations, a problem uncovered by this study is a false-positive rate of 8.3%. The seriousness of a false-positive result is dependent on the action taken after an abnormal test result. If the course of action is to perform a Gram stain of amniotic fluid, then a false-positive result is not clinically problematic. However, if the course of action is to deliver a preterm neonate believed to be infected, then there is the potential for serious consequences.

To examine the role of amniotic fluid glucose determinations in the rapid diagnosis of intraamniotic infection, we explored two diagnostic schemes: (1) simultaneous utilization with the Gram stain and (2) sequential use of both tests. Our data do not support the simultaneous use of both tests because the improvement in sensitivity is accompanied by a significant increase in the false-positive rate (from 0.7% to 9%).

The other alternative is to use the tests in sequence. The flow diagram provided in Fig. 3 displays the results of using a sequential diagnostic testing modality that incorporates amniotic fluid glucose determinations as a first-line test. A low glucose determination would have identified 15 of the 16 cases with positive Gram stains. Furthermore, a high glucose concentration has a high negative predictive value (97.8%).

Is there a role for this scheme of sequential testing in clinical practice? The Gram stain examination is the most widely used method for the rapid detection of bacteria in body fluids as it is rapid and inexpensive. However, Gram stain examination of amniotic fluid requires considerable experience. In a study conducted at our institution, considerable disagreement was found between results obtained by obstetric medical staff and trained laboratory personnel. Given the seriousness of the intervention implemented after identification of bacteria in a Gram stain, we concluded that Gram stain examinations of amniotic fluid should be read only by experienced laboratory personnel (Romero R, unpublished observations).

In most medical centers trained microbiology technicians are not available around-the-clock. Amniotic fluid glucose determination can assist the clinician in

deciding whether a Gram stain needs to be performed and analyzed immediately or whether it may be postponed until experienced personnel are available. In this context, amniotic fluid glucose determination has several advantages. The test is simple to perform and the required equipment is generally available in most obstetric units. Glucose determination is rapid, inexpensive, and does not require sophisticated interpretation by trained personnel.

The rapid diagnosis of infection in clinical medicine is a challenging problem. The approach used in other compartments, such as cerebrospinal fluid, consists of a combination of tests including the Gram stain, white blood cell and differential counts, and glucose and protein concentrations. A similar approach could be used for the detection of intraamniotic infection. Amniotic fluid glucose determinations may serve as an important component of this battery of tests. Further studies are required to explore the advantages and disadvantages of this approach. Other issues that need to be addressed are the effects of changes of amniotic fluid volume and maternal glucose intolerance on the clinical value of this test.

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False-negative syphilis screening: The prozone phenomenon, nonimmune hydrops, and diagnosis of syphilis during pregnancy

Kathleen Berkowitz, MD, Laxmi Baxi, MD, and Harold E. Fox, MD
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The prevalence of congenital syphilis is rapidly rising in several areas of the United States. Efforts to control the disease depend on the effectiveness of established screening strategies and treatment of infected pregnant women. False-negative test results hinder these efforts and leave the fetus at risk for acquiring congenital syphilis. Recently we encountered four cases of false-negative syphilis serologic results in women who gave birth to infants with congenital syphilis. The false-negative results were caused by the prozone phenomenon. The prozone phenomenon, seen during primary and secondary syphilis, occurs because a higher than optimal amount of antibody in the tested sera prevents the flocculation reaction typifying a positive result in reagin tests. Serum dilution is necessary to make the correct diagnosis. We recommend that for any pregnant woman with apparently negative syphilis serologic results in whom fetal compromise of unknown etiology exists, particularly nonimmune hydrops, nontreponemal testing should be repeated using serum dilutions to prevent a missed diagnosis of syphilis. We further recommend serum dilution as a routine procedure for all pregnant women in areas of high syphilis prevalence. (Am J Obstet Gynecol 1990;163:975-7.)

Key words: Prozone phenomenon, false-negative syphilis screening, serum dilution, screening strategies, nonimmune hydrops

A dramatic increase in the prevalence of syphilis has been noted in several areas of the United States during the past 2 years. The prevalence of congenital syphilis has also risen rapidly and in some areas is now considered epidemic.[1] Attempts to control this epidemic hinge on adequate surveillance, identification, and treatment of infected women.

The use of nontreponemal serologic tests is widely accepted as an effective screening strategy for the detection of syphilis during pregnancy. However, in some clinical situations difficulty in diagnosis results in misidentification of the true disease state despite the use of highly accurate tests. False-positive results have been reported in many conditions including pregnancy.[2-5] Serial testing, dark-field examination, or treponemal tests clarify the diagnosis in these situations. False-negative results may occur when the patient is tested long after treatment, during late-latent syphilis, or as a result of the prozone phenomenon. A false-negative error presents a serious problem because an infected woman would then fail to receive treatment, leaving her fetus vulnerable to the disastrous consequences of congenital syphilis.

The prozone phenomenon occurs when an excess of antibody in the sera being tested prevents the formation of the antibody-antigen lattice network needed to visualize a positive flocculation reaction.[6] Antibody may remain undetected if the antigen is too dilute or too concentrated. The zone of concentrations in which precipitation or flocculation can occur is called the "optimal zone." When a sample shows a negative reaction because of antibody-antigen concentrations outside the optimal zone, a "zonal reaction" or prozone phenomenon has occurred.[7] The term "sero-negative syphilis" was coined in 1950 to describe the effect.[8] The prozone phenomenon can affect any agglutination reaction and its first description in 1907[9] predates even the Wassermann complement fixation test. The prozone phenomenon can cause a false-negative result when Venereal Disease Research Laboratories or rapid plasma reagin tests are used and occurs in approximately 2% of cases of primary or secondary syphilis.[10] Serum dilution reestablishes the proper concentrations of antibody and antigen that allow lattice formation.

Four women with false-negative syphilis serologic results (Becton-Dickinson rapid plasma reagin card test, Rutherford, N.J.) gave birth to infants with congenital

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syphilis at the Sloane Hospital for Women in 1989. The false-negative results were caused by the prozone phenomenon. This article details their clinical presentations and the management difficulties encountered as a result of the prozone phenomenon.

Case reports

Case 1. A 26-year-old woman (gravida 8, para 3-0-4-2) was seen at 32 weeks' gestation with a complaint of decreased fetal movement. Rapid plasma reagin testing at 16 weeks of gestation and in previous years had been reported as negative. There was no maternal clinical evidence of syphilis. TORCH titers and a rapid plasma reagin test result were reported as negative on admission. Ultrasonography revealed bilateral hydrocele, polyhydramnios, and possible hydrops. During cordocentesis for karyotyping and acid-base determination, bradycardia and prolonged umbilical cord bleeding occurred that necessitated emergency cesarean section. A live-born male infant weighing 2525 gm with Apgar scores of 0 and 3 at 1 and 5 minutes was delivered. The infant had significant metabolic acidosis, thrombocytopenia, and physical signs of congenital syphilis. There was no cord hematoma. A second maternal serologic sample (Becton-Dickinson rapid plasma reagin card test) yielded an initial negative result and a positive titer of 1:64 on serum dilution; the treponemal test result was positive.

Case 2. A 21-year-old woman (gravida 3, para 1-0-1-1) at 32 weeks' gestation who had received no prenatal care was seen with malaise and decreased fetal movement. There was no clinical evidence of syphilis and she reported past negative serologic results. Fetal heart rate monitoring revealed a minimally reactive tracing. Amniotic fluid was increased and the placenta appeared edematous on ultrasonogram. Rapid plasma reagin and TORCH titers were reported as negative on admission. The original serum sample was diluted to evaluate a possible prozone phenomenon because of strong clinical suspicion of intrauterine infection. A cesarean section was performed for management of fetal distress. A male infant weighing 1460 gm with Apgar socres of 5 and 8 at 1 and 5 minutes was delivered. The infant had clinical and serologic evidence of congenital syphilis. Long-term follow-up of this infant is not available. Serum dilution titer was 1:256 with positive treponemal testing.

Case 3. A 36-year-old woman (gravida 6, para 4-0-1-0) was seen at term in active labor. She had no clinical or historical evidence of syphilis infection. A perineal lesion seen 1 week earlier was positive after culture for herpes simplex virus and a rapid plasma reagin test on admission was reported as negative. Fetal distress was seen on admission and a cesarean section delivery produced a male infant with Apgar scores of 1 and 1 at 1 and 5 minutes. The infant had petechiae, hepatosplenomegaly, thrombocytopenia, and died 7 hours post partum. Pathologic studies showed a pale and bulky placenta. Serum dilution yielded a postive titer of 1:128 with positive treponemal testing.

Case 4. A 30-year old woman (gravida 4, para 1-0-2-1) at 27 weeks' gestation had contractions and decreased fetal movement. She had received no antenatal care and had a history of adequately treated primary syphilis in 1986. The rapid plasma reagin test for syphilis on admission was negative despite physical findings including condyloma lata. Ultrasonography confirmed a 27-week intrauterine death with hydrops and placentomegaly. The patient was spontaneously delivered of a severely macerated, hydropic fetus weighing 2070 gm. Petechia, splenomegaly, and funisitis[11] were noted at autopsy and the placenta was bulky and pale. Serum dilution yielded a rapid plasma reagin titer of 1:256 with positive treponemal testing.

Comment

The laboratory diagnosis of syphilis can be made with darkfield microscopy or serologic testing. The mobile, corkscrew-shaped organisms of *Treponema pallidum* can be identified microscopically by examination of fresh exudate with a dark-field condenser. Serologic tests are divided into treponemal and nontreponemal tests. Treponemal tests detect antibodies against *T. pallidum* by incubation of the specimen with labeled anti–*T. pallidum* globulin (fluorescent treponemal antibody-absorption test) or sensitized sheep erythrocytes (microhemagglutinin test). The first treponemal test developed in 1949 was the *T. pallidum* immobilization test. It has been largely replaced by the more sensitive, less expensive tests mentioned earlier. The nontreponemal tests, such as the VDRL or rapid plasma reagin card test, use purified cardiolipin-lecithin-cholesterol antigen. The VDRL test requires heated serum and a positive result is determined microscopically by visualizing flocculation. The rapid plasma reagin card test and the automated reagin test use unheated serum and stabilized cardiolipin antigen suspended in charcoal. The results are read macroscopically as a result of agglutination. This approach has the advantage of being simpler to perform and standardize. When evaluating the efficacy of treatment by measurement of serum titers, the same nontreponemal test should always be used because there may be a marked variation in titers between tests. The nontreponemal tests generally are more sensitive in the diagnosis of primary syphilis, but in secondary syphilis there is no difference in sensitivity between nontreponemal and treponemal tests.[12] Treponemal tests are more sensitive in the diagnosis of tertiary syphilis.

The prozone phenomenon occurs when the amount of antibody in a particualr serum sample is too high to allow formation of the antibody-antigen complex necessary to visualize flocculation or agglutination. Syphilitic infection may be hidden in those patients whose serologic results are rendered negative by the prozone phenomenon. This is a particulary worrisome problem in asymptomatic pregnant women. Because the true

cause of fetal compromise is masked, the management of pregnancy and labor cound potentially be misguided. Diagnosis of congenital syphilis with its attendant risk of thrombocytopenia and anemia affect management of the timing and route of delivery. The last case illustrates that routine serologic study may be misleading in the diagnosis of inadequately treated or reacquired disease.

The predictive value and cost benefit of screening pregnant women for syphilis depends on the prevalence of the disease in the population being tested. Because the cost of treating infants with congenital syphilis is so high, screening and treatment of almost all populations of infected women is cost beneficial.[13] The prevalence of syphilis in the population of women who were delivered at the Sloane Hospital for Women in 1988 was 2.7% (140 cases in 5280 deliveries). Of the infants born to these women, at least seven (1.3 per 1000 deliveries) had symptomatic congenital syphilis. Approximately two thirds were asymptomatic but had serologic test results compatible with the diagnosis of congenital syphilis and required intravenous antibiotic therapy.

We recommend that serum dilution be performed to evaluate the possibility of a false-negative result caused by the prozone phenomenon for any woman with negative serologic results in whom intrauterine infection is suspected. Serum dilution should also be included in the workup of nonimmune hydrops. When clinically indicated, ultrasonography is helpful in discovering evidence of intrauterine infection such as placentomegaly, polyhydramnios, or intrauterine growth retardation. We further recommend that in populations with a high prevalence of syphilis every woman should have rapid plasma reagin testing with serum dilution on presentation for antepartum care and again in the third trimester.

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Intrapartum hepatitis B screening in a low-risk population

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Intrapartum hepatitis B surface antigen testing was performed on all laboring patients admitted to Forsyth Memorial Hospital in Winston-Salem, North Carolina from December, 1988 through November, 1989. Of the 5580 patients tested, eight patients had test results positive for hepatitis B surface antigen (overall prevalence rate of 0.14%). HBsAg was present in 0.3% of public patients and 0.08% of private patients. Of the seven patients who were not known to be positive for hepatitis B surface antigen before pregnancy, three had identifiable risk factors for hepatitis B virus. The time interval from birth to administration of hepatitis B immune globulin in the newborn averaged 13.3 hours. Patient cost per new case detected was $13,203. Intrapartum hepatitis B surface antigen screening with an assay performed once daily allows for timely administration of hepatitis B immune globulin to the newborn in accordance with recommendations of the American College of Obstetricians and Gynecologists, although some newborns receive hepatitis B immune globulin after the 12-hour birth-to-administration interval recommended by the Centers for Disease Control. (AM J OBSTET GYNECOL 1990;163:978-80.)

Key words: Hepatitis B virus, intrapartum screening, hepatitis B surface antigen

Vertical transmission of hepatitis B virus represents one of the most efficient modes of hepatitis B virus infection. In the United States an esimated 16,500 women who are positive for hepatitis B surface antigen (HBsAg) give birth yearly and approximately 3500 of their infants become chronic hepatitis B virus carriers.[1] Treatment of these newborns soon after birth with hepatitis B immune globulin and subsequently hepatitis B virus vaccine would prevent 85% to 90% of exposed infants from becoming chronic carriers.[2]

In June 1988 the Advisory Committee on Immunization Practices of the Centers for Disease Control recommended universal screening of all pregnant women early in the prenatal period[1] because studies from large inner-city hospitals found that only 35% to 65% of HBsAg-positive patients were identified by limiting screening to women considered high-risk by Advisory Committee on Immunization Practices guidelines.[3-5] These universal screening recommendations are based in part on prevalence rates in large inner-city hospitals. Although universal screening has been estimated to be cost effective in areas where the prevalence of hepatitis B virus infection is at least 0.06%,[6] many practitioners in hospitals outside inner-city areas remain reluctant to add the additional costs of routine hepatitis B virus screening to prenatal care. Practitioners are also concerned that maternal hepatitis B virus test results performed early in gestation are not available to the pediatrician early in the newborn period and are concerned about untested patients who are transferred at the onset of labor and patients who receive no prenatal care.

Because of these concerns we examined the feasibility and cost of universal hepatitis B virus screening at the time of labor in a non-inner-city population in western North Carolina by addressing three questions. (1) What is the prevalence of HBsAg-positive women in this population? (2) Will screening for HBsAg at the time of labor allow for timely immunization of the newborn? (3) What is the cost per case detected in this population?

Methods and material

Since December 1988 all patients in labor who came to Forsyth Memorial Hospital in Winston-Salem, North Carolina, have been screened for HBsAg. Approximately 5000 births per year occur at Forsyth Memorial Hospital to Forsyth county residents (which includes 94% of the total births from Forsyth County) and an additional 300 to 400 births per year occur at Forsyth Memorial Hospital to women transferred from the 19-county referral area surrounding Forsyth county. Patients are transferred to Forsyth Memorial Hospital to receive high-risk obstetric care from the Obstetrics Department of Bowman Gray School of Medicine of Wake Forest University. Winston-Salem has a population of 150,000. The largest city from which referrals are received, Greensboro, North Carolina, has a population of 200,000. Approximately 70% of the obstetric patients who are delivered at Forsyth Memorial Hospital are white, and 70% of the overall pa-

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Table I. Patients with positive HBsAg and neonatal hepatitis B immune globulin administration

Patient No.	*Type of prenatal care*	*Maternal risk factor*	*Known positivity before admission*	*Intervals (hr)*		
				Admission–result known	*Admission-birth*	*Birth–hepatitis B immune globulin given*
1	Private	Filipino	No	22.5	31.0	4.0
2	Public	None	No	19.0	4.0	18.0
3	Public	Intravenous drugs	No	17.0	137.0	0.5
4	Private	None	No	29.5	12.5	23.0
5	Public	None	No	17.0	6.0	13.0
6	Private	Korean	Yes	—	30.5	1.0
7	Public	Multiple sexually transmitted diseases	Yes	—	4.0	7.0
8	Public	None	No	32.0	14.0	21.0

tient population receive their care from private physicians. Eighty percent of patients who receive care from a private physician are white, and the majority of the remainder are black. The prevalence of illicit drug use and sexually transmitted diseases in the private group is unknown.

Except for selected situations, all Medicaid patients are seen and followed through local health departments by resident physicians from Bowman Gray School of Medicine. Therefore all patients seen by private physicians have private third-party coverage or are able to self-pay the physician's fee and hospital costs of delivery. Of the 30% of patients who receive their care through local health departments, approximately 55% are white, and the remainder black, with an occasional patient of Hispanic, Oriental, or Native American background as in the private population. The admitted use of illicit parenteral drugs is increasing in our public health department patients and currently appears to be in the 5% to 15% range. The prevalence of *Neisseria gonorrhoeae* infection at the first prenatal visit is 2% to 3%, and *Chlamydia trachomatis* 5% to 6%.

Patients were screened for HBsAg with the AUSRIA 11-125 radioimmunoassay (Abbott Laboratories, North Chicago). The assay was performed once daily and positive results (defined as counts ≥2.1 times the mean of the negative controls) were confirmed with standard hepatitis B profiles including hepatitis B e antigen (HBeAg), and antibodies to hepatitis B core, surface, and e antigens. Patients with a positive test for HBsAg were referred for infectious disease consultation and their infants received hepatitis B immune globulin (and hepatitis B virus vaccine) as soon after birth as test results were available.

Results

During the 12 months from Dec. 1, 1988, through Nov. 30, 1989, 5580 laboring patients were screened for HBsAg. Eight patients were found to be HbsAg-positive (prevalence of 0.14%). The rate in public patients was 0.3% and in private patients was 0.08%.

One of the eight patients was Korean and a known chronic hepatitis B virus carrier and one had been found to be HBsAg–positive at a previous admission for preterm labor (patients 6 and 7, respectively, Table I). The remaining six were not known to be positive for HBsAg before labor. Four of the six (67%) had no known risk factors for hepatitis B virus infection as defined by the Advisory Committee on Immunization Practices.[3] Three of these four previously unknown HBsAg-positive patients were public health department patients and one was a private patient.

In the six patients not known to be positive for HBsAg at the time of admission, the average time from admission in labor until HBsAg results were known was 23 hours (range, 17-32 hours) (Table I). The time interval from birth to administration of hepatitis B immune globulin averaged 13.3 hours (range, 0.5 to 23.0 hours).

The actual hospital cost of each HBsAg assay was $12.90, for a total cost of $71,982 for the 12 months studied. Actual cost per new case detected (excluding the one patient previously known to be a chronic carrier) was $10,283. The cost to the patient of the HBsAg test used for screening was $15 per patient for the first 6 months, and $18 for the last 6 months, for a total cost of $94,421 for the 12-month period. The cost per new case detected (excluding the one patient previously known to be a chronic carrier) was $13,488 per case.

Comment

Infants born to women positive for HBsAg (and hepatitis B e antigen) have a 90% risk of hepatitis B virus infection. Ninety percent of infected infants become chronic carriers at risk for the development of cirrhosis and hepatocellular carcinoma.[1] The development of the carrier state can be prevented in 85% to 90% of infants born to HBsAg-positive mothers by prompt administration of hepatitis B immune globulin after birth

and a series of hepatitis B virus vaccine injections.[2] Whereas infants are at highest risk for hepatitis B virus infection when the mother is both HBsAg- and HBeAg-positive,[7] fatal cases of hepatitis B virus infection have been reported in infants of HBsAg-positive, HBeAg-negative mothers,[8] and infants born to HBsAg-positive women should receive immunization regardless of maternal HBeAg status.

Current Centers for Disease Control recommendations include universal screening of all pregnant women for hepatitis B virus infection early in gestation as well as availability of HBsAg results within 24 hours for women admitted in labor who have not had prenatal screening.[1] Prompt treatment of the infant after birth then can occur. In large inner-city populations with high prevalence rates of hepatitis B virus, these recommendations are generally considered appropriate. In other areas where the prevalence of hepatitis B virus is lower, the cost effectiveness of universal screening may be questioned because of the presumed low likelihood of positive results. Logistically, transmitting HBsAg information from the maternal physician's office to the pediatrician at the time of birth may impede timely hepatitis B immune globulin administration to the infant, and centers that receive transfer patients or patients without prenatal care may have substantial numbers of patients in labor who have not been screened early in gestation. An occasional HBsAg-negative patient in early pregnancy may acquire hepatitis B virus during pregnancy with minimal symptoms.

On the basis of the 5580 patients in this study, intrapartum HBsAg testing of all patients with an assay performed once daily, while obviating the need for screening in early pregnancy, will not allow reporting of every patient's HBsAg status within 24 hours of admission nor will it allow for administration of hepatitis B immune globulin to exposed infants within 12 hours of birth as recommended by the Centers for Disease Control.[1] Two of the six infants born to women not known to be HBsAg-positive at the onset of labor received hepatitis B immune globulin within 12 hours of birth and four received hepatitis B immune globulin more than 12 hours (13, 18, 21, and 23 hours, respectively) after birth (Table I). The apparent decline in efficacy of hepatitis B immune globulin as the interval from birth to administration increases was the basis for the Centers for Disease Control recommendation of administration of hepatitis B immune globulin within 12 hours of birth.

The population base and regional characteristics of our patients would suggest a low-risk group for hepatitis B virus infection, and the 0.14% prevalence is slightly lower than the national average of 0.2%.[6] When the prevalence is at least 0.06%, direct and indirect costs of universal antepartum screening as well as immunization of the newborn allow for a cost-effective prevention program.[6] Shifting the time of screening to the intrapartum period allows for continued cost effectiveness while obviating the logistic problems described above.

Universal intrapartum HBsAg screening in this low-risk population identified seven previously undetected HBsAg-positive women (four without any identifiable risk factors for hepatitis B virus). This approach permitted timely immunization of their infants with hepatitis B immune globulin (and subsequently hepatitis B virus vaccine). However, once-daily performance of the HBsAg assay did not permit strict adherence to the Centers for Disease Control recommendations to obtain all HBsAg test results within 24 hours of admission or administration of hepatitis B immune globulin to the infant within 12 hours of birth.

These findings must be considered in planning of policies for screening pregnant women for hepatitis B virus infection. Hospitals without daily HBsAg testing capabilities should continue to consider prenatal testing of their obstetric patients.

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Risk factors associated with the increasing prevalence of pneumonia during pregnancy

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A retrospective chart review of 1120 antepartum admissions revealed the prevalence of antepartum pneumonia rose to 1 per 367 deliveries. A total of 26 cases in 9560 deliveries were identified with criteria of fever >39° C, productive cough, and radiologic findings of infiltrates or consolidation. Pregnancy-related outcome variables studied were prevalence of preterm labor or birth, birth weight, and trimester of occurrence. Pneumonia characteristics studied were rate and type of organisms recovered, seasonality, and severity of the illness and radiologic findings. Exposure variables relating to the development of pneumonia studied were underlying medical conditions, hematocrit, human immunodeficiency virus status, and drug use. Birth weight, hematocrit, human immunodeficiency virus status, and drug use were compared with a randomly selected sample of women drawn from the general population delivered of infants during the study time period. One patient experienced preterm delivery, which occurred 1 month after cure of pneumonia. Birth weight was significantly lower in the study group (2770 ± 224 gm versus 3173 ± 99 gm, $p < 0.01$). The most common organism recovered was *Streptococcus pneumoniae*. A total of 42% of patients had multilobar involvement and two required intubation. Cocaine use (52% in the study group versus 10% in the general population, $p < 0.01$) and human immunodeficiency virus positivity (24% in the study group versus 2% in the general population, $p < 0.01$) were significant risk factors for antepartum pneumonia. (Am J Obstet Gynecol 1990;163:981-5.)

Key words: Pneumonia, human immunodeficiency virus status, drug use, pregnancy outcome

The morbid complications of antepartum pneumonia have markedly changed since the introduction of antibiotic therapy. In the preantibiotic era preterm labor and maternal mortality were frequent sequelae of pneumonia.[1, 2] Since the use of antibiotics began, maternal mortality has significantly decreased.[3, 4] The effect of antibiotic therapy on the prevalence of preterm labor has variably been reported as decreased[3] or unchanged.[5] The prevalence of antepartum pneumonia has fallen from a rate in the preantibiotic era (before 1956) of 1 per 118 deliveries[2] to 1 per 2288 deliveries.[3] The most recent case review reported a slightly increased rate of 1 per 1287 deliveries.[5]

In the past 5 years drug use and human immunodeficiency virus (HIV) infection have dramatically increased in certain populations of pregnant women. Previous large studies have not examined the effect of these problems on the epidemiologic factors, pathophysiology, and morbidity of pneumonia in pregnancy. This study was designed to discover whether recent changes have occurred in the cause, morbidity, or sequelae of antepartum pneumonia as a result of HIV status or drug use. We reviewed all cases of community-acquired pneumonia diagnosed during pregnancy at the Sloane Hospital for Women in 1988 and 1989 to determine the pathogenesis and risk factors involved in the development of this disease.

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6/6/22588

Material and methods

Discharge diagnostic chart coding was reviewed for 1120 antepartum admissions to the Sloane Hospital for Women from January 1988 to November 1989. The Sloane Hospital for Women is a tertiary care university hospital in New York City, serving a large indigent population and delivering more than 5000 infants per year. A total of 213 charts in which the diagnosis was related to respiratory complaints, "fever," or was unclear underwent extensive chart review. With inclusion criteria of productive cough, radiologic findings of infiltrates, and fever >39° C, 26 cases of pneumonia were identified in 25 patients. Alternative sources of information including review of residency experience logs did not yield any cases of pneumonia.

Exposure variables, outcome variables, and characteristics of the pneumonia were examined. Pregnancy-related outcome variables were birth weight, trimester of occurrence, and prevalence of premature labor or delivery. Pneumonia characteristics studied were rate

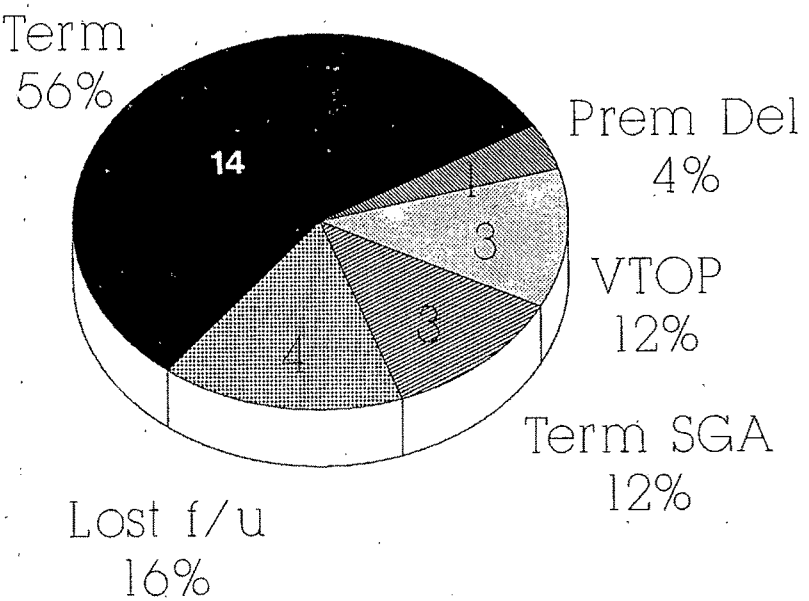


Fig. 1. Pregnancy outcome in 25 patients with pneumonia. *Prem Del,* premature delivery; *VTOP,* voluntary abortion; *f/u,* follow-up.

of recovery, type of organisms cultured, radiographic findings, seasonality, and severity of the illness. Exposure variables thought to affect susceptibility to pneumonia—underlying medical conditions, hematocrit, drug use as determined by urine toxicology screens, and HIV status—were examined.

Comparison groups were randomly selected from women cared for and delivered of infants at the Sloane Hospital for Women during the study period. The birth weight comparison group was selected by recording the second entry on each of 100 successive pages of the delivery room log. Hematocrit comparisons were obtained from the first prenatal visit data of randomly selected women first seen at the Sloane High-Risk Clinics for antepartum care. There was no significant difference in the percentage of values obtained during the second or third trimester between the groups. The comparison groups for HIV status and frequency of drug use were derived from independent studies conducted in the same population during the same time period covered by this study. Urine toxicology data were obtained from all women first seen in active labor (Unpublished data). Anonymous serosurveys conducted at the Sloane Hospital for Women in 1989 of women who required venipuncture in the delivery room were used to determine the HIV positivity rate in the general population. Statistical comparisons were made with the two-tailed paired Student t test, χ^2, and the Fischer exact test where appropriate.

Results

Pregnancy-related outcome variables. No cases of premature labor or delivery occurred during the hospitalization for pneumonia. Seventeen pregnancies reached term without premature labor, including two sets of twins. One patient had premature labor with unsuccessful tocolysis approximately 1 month after adequate treatment and resolution of the pneumonia. Four were lost to follow-up and three were voluntarily terminated (Fig. 1). Birth weight was significantly less in patients with antepartum pneumonia than that in the comparison group (2770 ± 224 gm versus 3173 ± 99 gm, $p < 0.01$, see Fig. 2). Few cases of pneumonia were diagnosed in the first trimester (Fig. 2).

Pneumonia characteristics. Fifteen cases occurred from September to January. There were no cases during the summer months of July or August (Fig. 3). Many patients (42%) had multilobar involvement with the lower lobes being most frequently involved (Fig. 4). Sputum cultures were positive in 27% of patients and blood cultures were positive in 15%. Viral cultures were not obtained. The most common organism identified in sputum cultures were *Streptococcus pneumoniae* (six cases) and it was the only organism recovered in blood cultures. Other pathogenic organisms recovered included *Haemophilus influenzae, Legionella pneumophila, Mycobacterium avium* complex, and *Mycoplasma* (Table I). In one patient who had community-acquired antepartum pneumonia, *Pneumocystis carinii* was recovered 1 month post partum. The episode was not included for analysis in this study because it occurred post partum. Eighteen patients required supplemental oxygen. Complications of bronchospasm that required intubation developed in two patients with a history of asthma. In each case the patient was extubated within 24 hours. Empiric antibiotic therapy with cefoxitin or cefuroxime

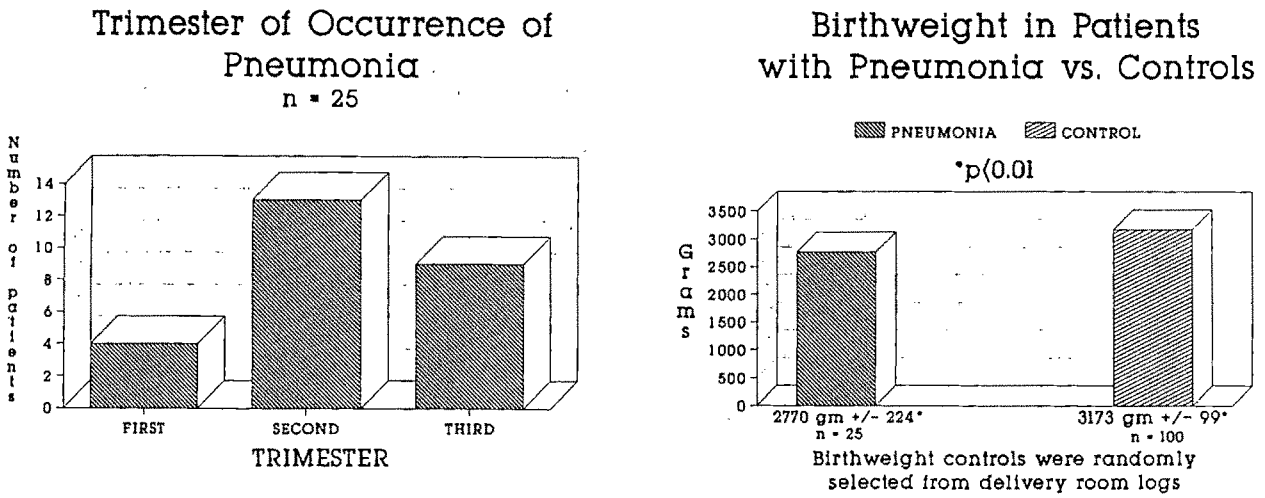


Fig. 2. Trimester of occurrence and infant birth weight in patients with pneumonia.

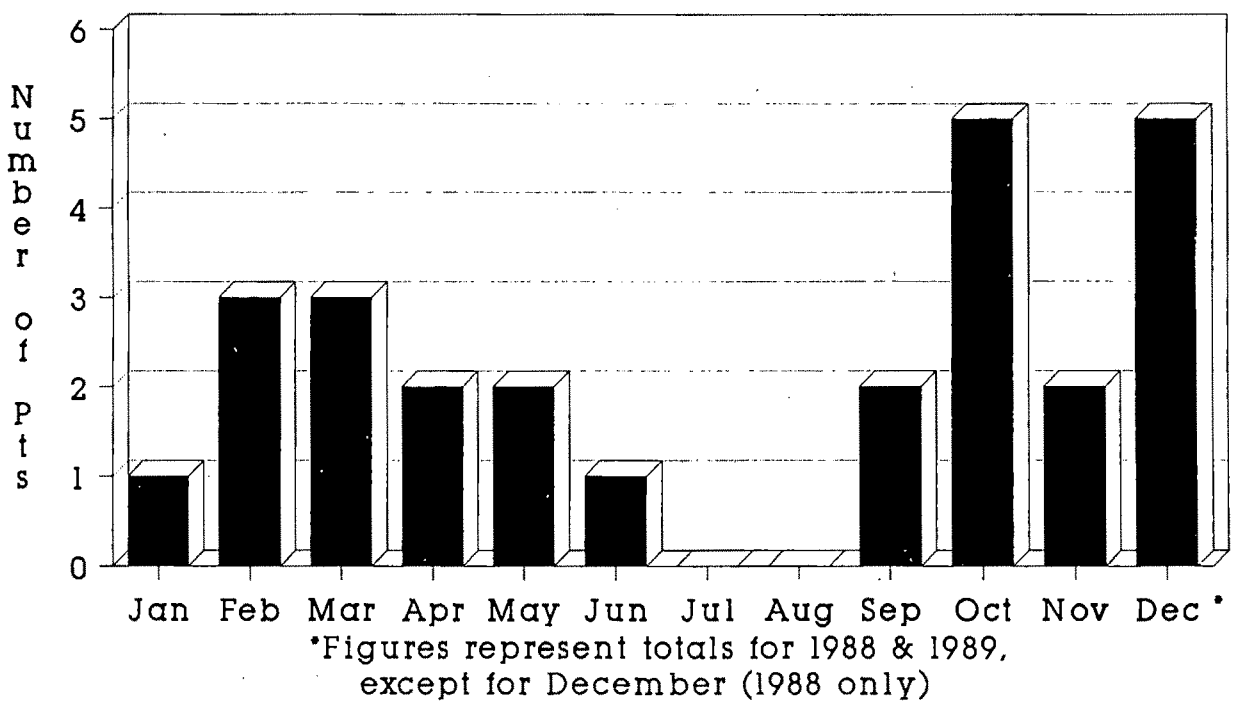


Fig. 3. Seasonal incidence of antepartum pneumonia.

and erythromycin was begun in all patients. When cultures were positive, therapy was changed to the most appropriate antibiotic. Three patients received trimethoprim-sulfa. Most patients were observed to defervesce by the third day of therapy. The average length of hospitalization was 8.4 days.

Exposure variables. Ten patients had underlying medical conditions including iron deficiency anemia, history of asthma or tuberculosis, or previous episode of pneumonia. Hematocrit was significantly lower in study patients than in the comparison group (31.5% ± 0.95% versus 34.9% ± 0.90%, $p < 0.01$, see Table II). Drug use was determined by urine toxicology screening and when positive was documented as cocaine without exception. The study group had a significantly higher percentage of positive urine toxicology screening results (52% versus 10%, $p < 0.01$, see Fig. 5). Patients who used cocaine reported that their preferred method of drug ingestion was smoking either cocaine or "crack" cocaine. HIV status was determined in 11 cases and three were positive. Three had other evidence of HIV positivity such as altered T-cell ratios

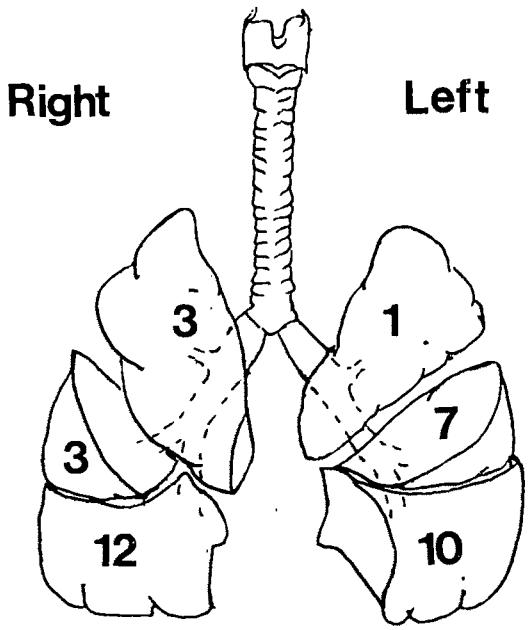


Fig. 4. Radiologic findings of lobar involvement. A total of 42% of patients (n = 25) had multilobar involvement, with the lower lobes most often affected.

Table I. Pathogens recovered in antepartum pneumonia

Organisms identified		*Positive cultures*	
Streptococcus pneumoniae	6	Sputum	27%
Haemophilus influenzae	2	—	—
Legionella	1	Blood	15%
Mycoplasma	1	—	—
Mycobacterium avium complex	1	—	—

S. pneumoniae was the only organism identified in blood cultures. *Pneumocystis carinii* was recovered from one patient postpartum.

or opportunistic infection concurrent with pneumonia. HIV positivity and T-cell function abnormalities were significantly higher in the study group than in the comparison group (24% versus 2%, $p < 0.01$, see Fig. 5).

Comment

The prevalence of antepartum pneumonia has steadily declined from 1939 to 1982 with the advent of antibiotic therapy. This study documents a sevenfold higher prevalence of pneumonia as compared with the recently published rate of 1 per 2288 deliveries.[3] This increase is observed against the background of a changing obstetric population. Greater numbers of women with chronic respiratory disease, an immunocompromised state, or drug addiction are achieving pregnancy. Several patients in this study were severely ill and required prolonged intravenous antibiotic therapy to adequately treat sepsis and multilobar involvement. Two required ventilatory support. Such hospitalizations place a great strain on already overused critical care resources and funds.

Table II. Medical conditions associated with pneumonia

	No. of patients	%
Medical condition		
Asthma	6	—
History of pneumonia	4	—
History of tuberculosis	2	—
Iron deficiency anemia	3	—
Average hematocrit		
Study (n = 25)*	—	31.5 ± 0.95
Control (n = 100)*	—	34.9 ± 0.90

Controls were randomly obtained from patients receiving care in the Antepartum High Risk Clinic.
*p <0.01.

The finding of significant anemia is in agreement with the findings of Benedetti[3] and reflects the general poor health and nutritional status of the patients in this study. Multiple underlying medical conditions, anemia, and HIV positivity were common. There were no maternal deaths recorded despite the abundance of poor prognostic factors already mentioned. Early aggressive use of antibiotics and advanced respiratory support therapies certainly contributed to the absence of maternal mortality.

There were no episodes of preterm labor during acute hospitalization for pneumonia. Two sets of twins reached term. There was one preterm delivery that was unrelated to the episode of pneumonia. The scarcity of preterm labor in this study was not expected given the severity of illness, but might be a result of early treatment of the disease. Whereas infants were significantly smaller than those in the general population, only three met small-for-gestational-age criteria. A multivariate analysis would have helped to elucidate the exact causes of decreased birth weight but the small number of subjects in this study precluded such analysis. There were no neonatal deaths. Analysis of neonatal length of hospital stay was not performed because many of these infants were housed in the hospital awaiting placement by the Bureau of Child Welfare. Long-term follow-up is not available at this time.

The etiologic agents traditionally associated with community-acquired pneumonia were also those most commonly recovered in this study. The only documented *Pneumocystis carinii* infection occurred in a patient who had previously had *Streptococcus pneumoniae*. HIV positivity and cocaine inhalation were highly significant risk factors and the mechanisms by which they increase host susceptibility have not been completely investigated.

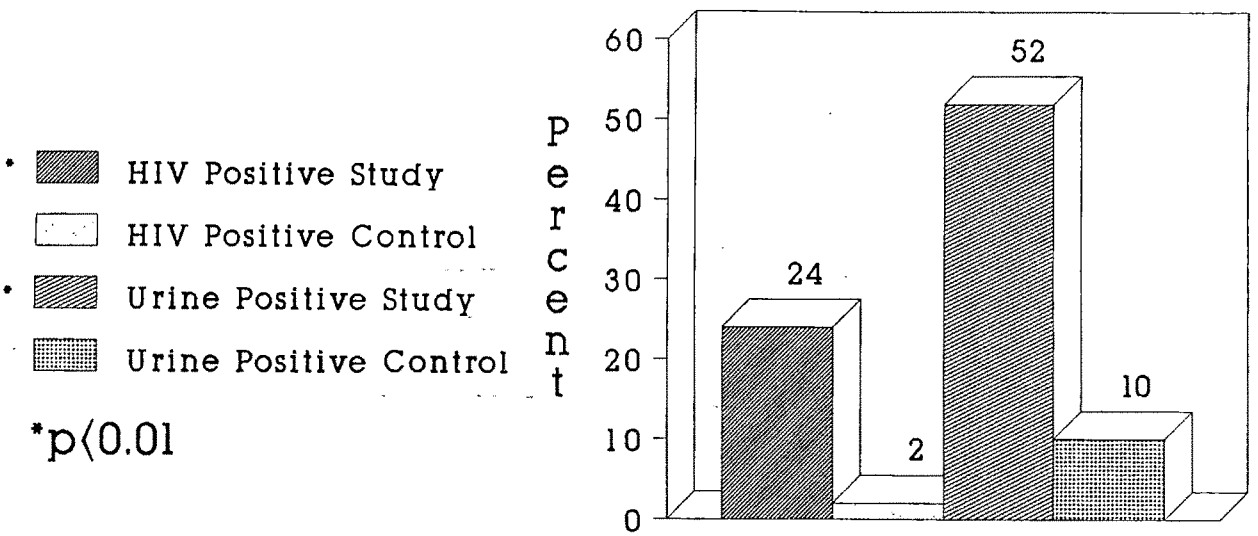


Fig. 5. HIV status and drug use in patients with pneumonia versus controls.

Cocaine inhalation can cause acute pulmonary edema and increased susceptibility to ordinary pneumonia,[6] probably through increased pulmonary capillary permeability. The "crack lung" syndrome is characterized by transient pulmonary infiltrates, fever, eosinophilia, and elevated immunoglobulin E levels.[7] Decreased diffusion across the alveolar membrane has been reported.[8] Another mechanism by which cocaine inhalation may increase host susceptibility is through formation of talc or cellulose granulomas in lung tissue.[9]

HIV positivity was significantly higher in the study group than that in the general population. It is interesting to note that three of the HIV-positive patients were previously in good health and asymptomatic at the time they contracted pneumonia. Common bacterial infections have been reported as the most frequently encountered pulmonary problem in drug users.[10] It may be postulated that T-cell dysfunction is manifested very early by impaired ability to encapsulate gram positive organisms, thus increasing a patient's susceptibility and morbidity to pneumonia.

Modern medical therapy has continued to suppress morbidity and mortality in patients with antepartum pneumonia. However, the increasing incidence and severity of pneumonia in pregnancy requires greater use of fixed medical resources and funds to maintain a low complication rate. The etiologic agents involved in pneumonia do not seem to have changed significantly. The epidemiology and pathophysiology of the disease have been altered by changing characteristics of the obstetric population. More pregnant women are susceptible to community-acquired pneumonia today because of chronic medical conditions, cocaine addiction, and HIV positivity. The clinician faced with such a patient must act quickly and aggressively to prevent significant maternal or obstetric complication.

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Ultrasonographic fetal weight estimation by an integrated computer-assisted system: Can each laboratory improve its accuracy?

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Estimated fetal weights from 1684 cases with singleton, live infants born within 7 days of an ultrasonographic examinations were compared with their birth weights, which ranged from 520 to 5920 gm. Estimated weight calculated from Shepard's equation produced a linear relationship of birth weight against estimated weight with an intercept and slope of 209.5 gm and 0.929. Overall, 75% of the estimated weights were within 15% of the actual weight. A separate regression model that used the same variables from Shepard's equation failed to improve the comparison between estimated and actual weights. All cases were reevaluated with multiple regression modeling. Various examination-to-birth intervals were analyzed; intervals ≤3 days appeared optimal. The best equation increased the percent of cases that were within 15% of the actual birth weight to 80%. The plot of birth weight against estimated weight had an intercept and slope of 33.1 gm and 0.994. Unlike Shepard's equation, the best equation was not statistically different from the ideal one-to-one relationship between estimated and actual weight. When the new equation was applied to an additional 339 new cases, equally accurate results were obtained. Customizing a laboratory's ultrasonographic weight estimation equations may be necessary to obtain the best estimate of fetal weight. (Am J Obstet Gynecol 1990;163:986-95.)

Key words: Fetal weight estimation, computer analysis

Obstetrics has changed from validating the accuracy of ultrasonographic parameters by clinical dating criteria to validating the accuracy of the last menstrual period by an ultrasonographic examination.[1] With improving neonatal survival and increasing reliance on ultrasonography for clinical management, it is necessary to know the accuracy of ultrasonographic weight predictions. Several authors have proposed equations for estimation of fetal weight but few are based on more than 100 patients,[2-5] including some equations for fetal weight estimation that have become standards.[6-8] Many institutions use published weight estimation equations to calculate fetal weights. When Shepard's equation of weight estimation was compared between New Haven, Connecticut, and Dallas, Texas, different coefficients were needed to ensure the best correlation between the estimated weights and the birth weights for the two populations.[9] The purpose of this study was to evaluate the accuracy of our ultrasonographic fetal weight estimations by comparing them with actual birth weights to derive an institutional equation for ultrasonographically estimating fetal weight.

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6/6/22587

Methods

This study included all singleton pregnancies without congenital fetal abnormalities delivered between January 1983 and September 1989 at Strong Memorial Hospital, Rochester, New York, within 7 days of an ultrasonographic examination performed in our Perinatal Ultrasound Laboratory. These cases were used to determine the accuracy of ultrasonographic fetal weight estimation. Cases with complete ultrasonographic parameters (abdominal circumference [AC], biparietal diameter [BPD], and femur length [FL]) were included in the second part of the study to determine our population's best equation for fetal weight estimation. This equation was confirmed again by performing the calculations as a true cross-sectional study.

Each ultrasonographic examination was handled as an independent estimation. All examinations were performed with either a Technicare 280SL or a Corometrics 650. Multiple measurements were made for each parameter (BPD, AC, FL) with a Summa/IBM Digital Image Quantification System. For each measurement the program, written by the Perinatal Computer Center staff, checks the calibration and calculates the mean, standard deviation, and deviation from the mean for

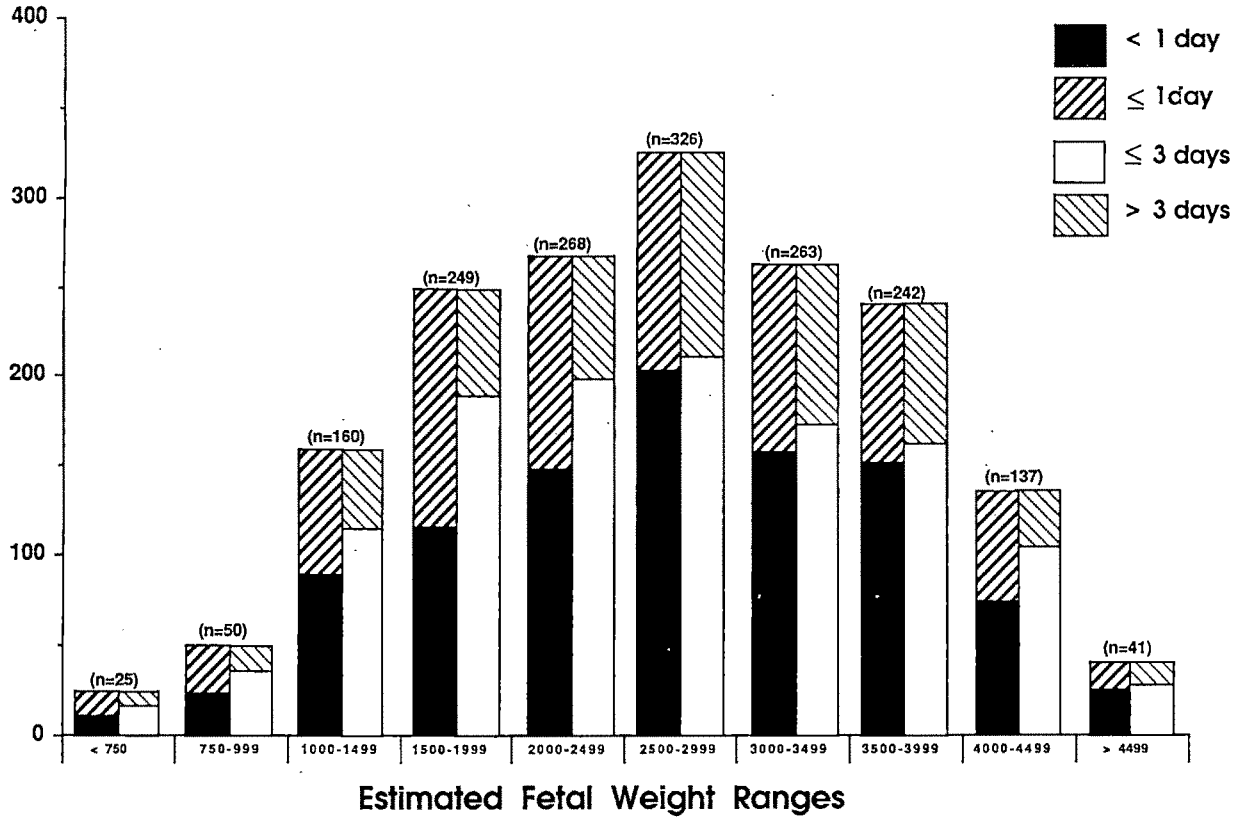


Fig. 1. Distribution of the total population (≤7 days) that has been subdivided by the examination-to-birth interval. Note the ≤1000 gm group has been subdivided by 250 gm intervals rather than 500 gm.

that parameter. The weight was estimated with mean AC and BPD in Shepard's equation (equation 1): Log_{10} (estimated weight) = − 1.7492 + 0.166/(BDP) + 0.046(AC) −2.646(AC × BPD)/1000.[6] The program does not calculate an estimated weight that is based only on abdominal circumference or in the absence of a normal head shape (cephalic index between 0.7 and 0.86). All measurement means and calculated values are stored in the Obstetrical Ultrasound Database. The delivery data were entered into the Perinatal Computer Database and merged with the Obstetrical Ultrasound Database.

The population was divided into groups by their estimated weights (Fig. 1), and by the examination-to-birth interval. The total population and groups were divided by the absolute value of the weight difference (|Estimate − Actual|) (Fig. 2, *A*) and the absolute percent difference (|Estimate − Actual|/Estimate × 100) (Fig. 2, *B*). The estimated fetal weight was used as the independent variable because it is the known variable before delivery and is used in clinical decisions. To determine if a shorter examination-to-birth interval would improve the predicted fetal weight, an analysis of the original population by examination-to-birth interval was performed twice, once between ≤1 day and >1 day and again between ≤3 days and >3 days. The ≤1-day group was a subset of ≤3-day group. The statistical analysis consisted of linear regression, χ^2 analysis, and unpaired *t* tests using the SPSS/PC+ 2.0 statistical package for the total population and subgroups.

To determine the institutional weight estimation curve, values for BPD, AC and FL, their multiplicative products, and their logarithmic transformations were entered into multiple regression computer models in a forward stepwise fashion. The same variables used in Shepard's equation (equation 1) were entered into a separate regression model, equation 2. The equations from the regression models were evaluated by adjusted coefficients of determination (adjusted R^2) and standard error. The new estimated weights from the models were compared with the actual birth weights using a paried *t* test and linear regression. The slopes of birth weight against estimated weight were compared using the *t* test of the regression coefficients with separate variances.[10] Comparisons of the slopes were made between the models, to equation 1, and to the ideal one-to-one relationship of the actual and estimated weights. This comparison was made for the total pop-

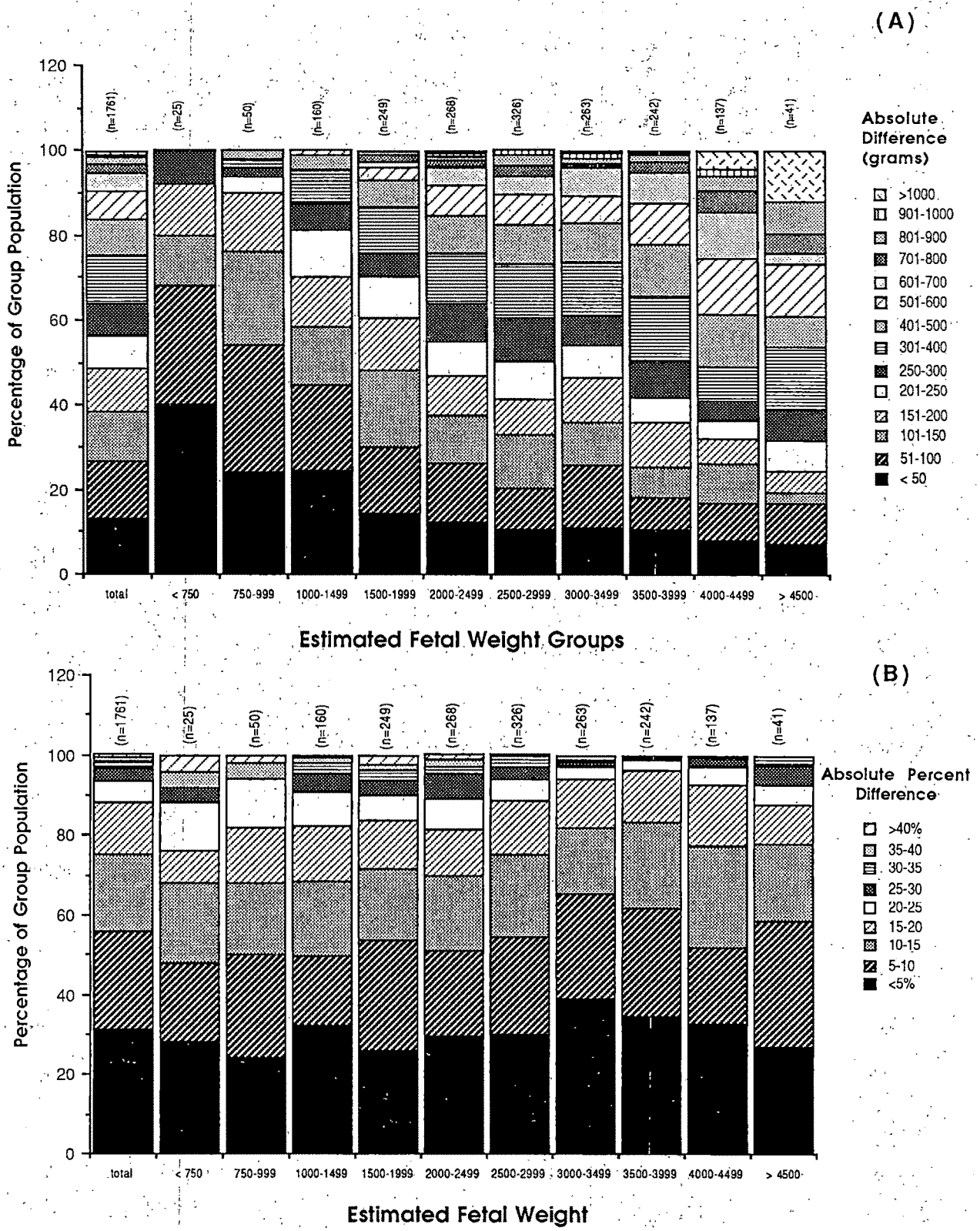


Fig. 2. Distribution of the absolute differences between the actual and estimated fetal weight as calculated from Shepard's equation ($n = 1761$), by the estimated fetal weight groups. **A**, Absolute weight difference in grams (Estimate − Actual); χ^2; $p < 0.0001$. **B**, Absolute percent difference (|Estimate − Actual|/Estimate); χ^2; $p = 0.002$.

Table I. Comparison of regression models for retrospective portion of study*

Equation no.	Regression model: Equation	n	Adjusted R^2	Examination-to-birth interval (days)	Standard error	Actual birth weight vs estimate ($y = ax + b$): Intercept	Slope	R^2	SE of slope	t Test comparison to ideal: t	p
1	Log 10 (est. wt.) = 1.7492 + 0.166/(BPD) + 0.046(AC) + −2.646(AC × BPD)/1000	1781		≤7		200.9	0.929	0.876	0.00836	7.25	<0.001
		1192		≤3		184.1	0.923	0.883	0.00974	7.87	<0.001
		567		>3		320.0	0.910	0.856	0.0157		
		704		≤1		171.2	0.920	0.879	0.0129	6.13	<0.001
		1055		>1		269.6	0.917	0.869	0.0110		
1	Cases with complete BPD, AC, and FL data	1684		≤7		202.7	0.926	0.877	0.00847	8.56	<0.001
		1134		≤3		173.0	0.927	0.883	0.0100	7.24	<0.001
		550		>3		309.7	0.912	0.861	0.0157		
		670		≤1		164.6	0.923	0.878	0.0133	5.78	<0.001
		1014		>1		256.1	0.920	0.873	0.0111		
2	Log 10 (est. wt.) = 3.4757 − 7.110(BPD) + 0.00345 (AC) + −0.119 (AC × BPD)/1000	1684	0.9103	≤7	0.0568	75.4	0.979	0.879	0.00865	2.46	0.014
3	Log 10 (est. wt.) − 2.32236 + 1.3704 log 10 (AC) + 0.9661 log 10 (BPD) + 0.76839 log 10(FL)	1684	0.9249	≤7	0.0517	64.9	0.982	0.891	0.00838	2.19	0.029
4	Log 10 (est. wt.) = −3.332022 + 1.32315 × Log 10 (AC × FL × BPD) + 0.000365234 FL × BPD	1684	0.9252	≤7	0.0517	2.84	1.006	0.893	0.00849	0.66	0.509
5	Log 10 (est. wt.) = −2.88128 + 1.22263 × Log 10 (AC × FL × BPD) − 0.000366593 (FL × BPD) + (2.71105 × 10^{-5}) × (AC × BPD)	1684	0.9256	≤7	0.0515	33.1	0.994	0.893	0.00838	0.75	0.453
		1134		≤3		2.48	0.994	0.903	0.00967	0.63	0.529
		550		>3		129.0	0.983	0.871	0.0161		
		670		≤1		−2.39	0.988	0.904	0.0125	0.93	0.352
		1040		>1		77.2	0.990	0.883	0.0113		

*Comparison by t test of the regression coefficient. When the slopes of equations 1 and 5 were compared, a t value of 5.56 ($p < 0.0001$) was obtained.

ulation and between the two examination-to-birth intervals (Table I). Further statistical analyses were performed on the estimated weights from the equation that had the best correlation between actual and estimated weight, based on the coefficient of determination (R^2), slope, and standard error of the slope.

To evaluate the hypothesis that the new weight estimation equation would represent our population better than Shepard's equation (equation 1), patients who were delivered at Strong Memorial Hospital within 7 days of an ultrasonographic examination, between October 1988 and May 1989, were evaluated prospectively. Those cases with complete ultrasonographic parameters meeting the same requirements as the initial population underwent weight estimates with Shepard's equation and our best new equation, equation 5. This population was evaluated and a full statistical analysis was performed on each set of estimates as in the initial population.

Results

The Perinatal Computer Database initially identified 1761 consecutive cases that met the study criteria. There were 1194 cases delivered within 3 days of an examination, including 706 cases born within 1 day. The birth weights ranged from 520 to 5920 gm, with a mean of 2704 ± 23.5 gm (mean ± SEM). The estimated weights, calculated from Shepard's equation, ranged from 556 to 6309 gm (mean, 2694 ± 23.8 gm). The mean absolute differences by weight and percent were 271 ± 5.48 gm and 10.51% ± 0.20%.

The distributions of the absolute differences in percent and grams differed significantly from one estimated weight group to another (X^2; $p = 0.002$ and $p < 0.0001$, respectively) (Fig. 2). The actual birth weights were more often within 100 gm of the estimate at the lower weights than at the higher weights (Fig. 2, *A*). Although the distribution of the absolute percent difference was statistically significant for the weight groups (Fig. 2, *B*), the overall distribution was more symmetric than the absolute weight differences (Fig. 2, *A*), which allowed for easier comparisons between weight groups.

There was a significant linear relationship between birth weight and ultrasonographically estimated weight (equation 1, Table I) with a slope of 0.929 and an in-

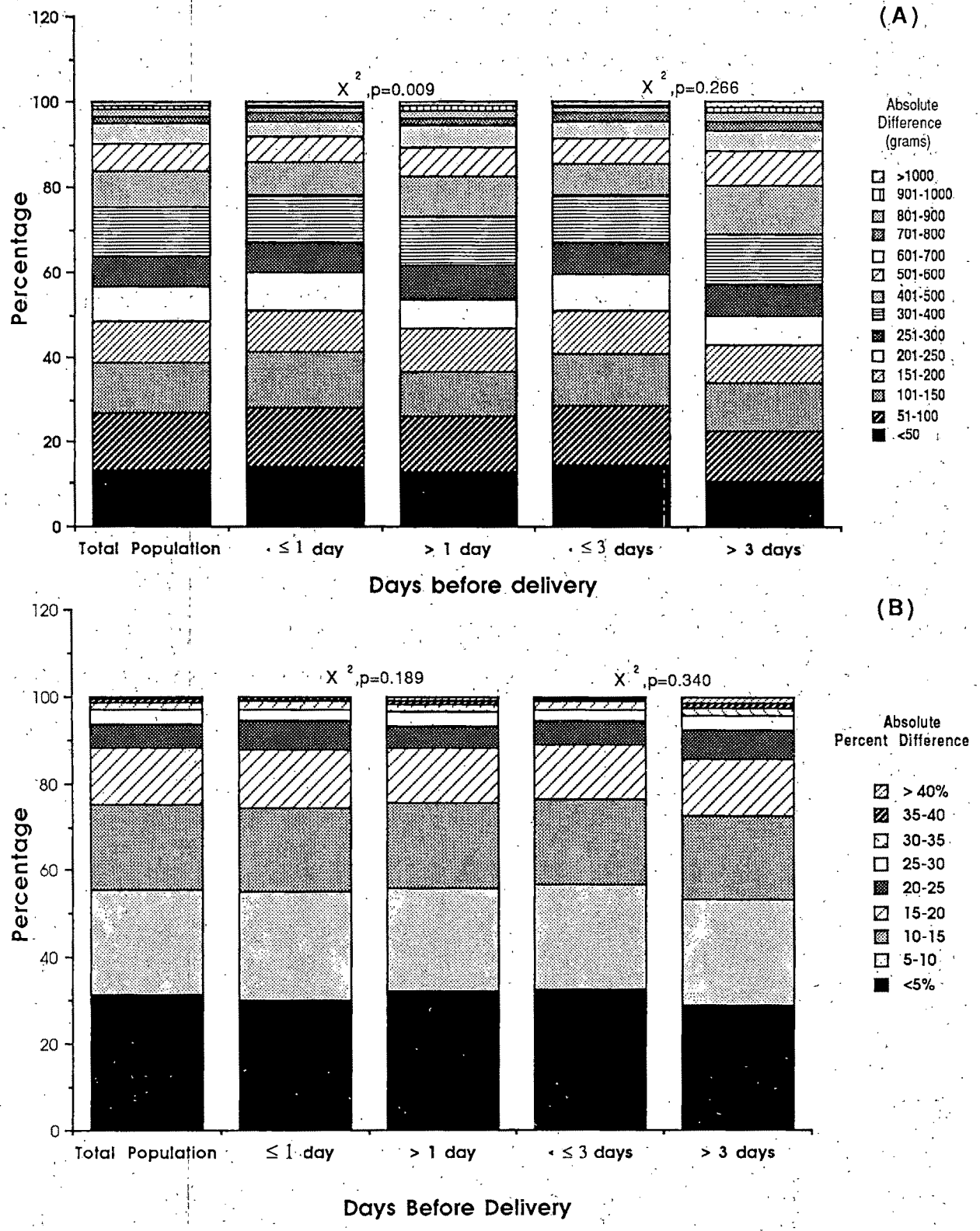


Fig. 3. Distribution of the absolute differences between the actual and estimated weights as calculated from Shepard's equation by examination-to-birth intervals. **A**, Absolute weight difference in grams (Estimate − Actual). **B**, Absolute percent difference (|Estimate − Actual|/Estimate).

Table II. Retrospective and prospective evaluation

Examination-to-birth interval	*Birth weight (gm) (Mean ± SEM)*	*Estimated fetal weight*	*Absolute differences*	
			%	*gm*
Retrospective evaluation				
Equation 1 (n = 1684)				
≤7 days	2703.8 ± 24.0	2696.6 ± 24.3	10.45 ± 0.202	270.3 ± 6.54
Paired t test	Est. vs BW; p = 0.400			
≤3 days	2596.0 ± 28.8	2612.4 ± 29.2	10.10 ± 0.210	255.7 ± 6.62
Paired t test	Est. vs BW; p = 0.103			
>3 days	2926.2 ± 41.8	2870.1 ± 42.5	11.16 ± 0.374	300.5 ± 9.95
Paired t test	Est. vs BW; p = 0.001			
Unpaired t test to ≤3 days	p < 0.001	p < 0.001	p = 0.012	p < 0.001
≤1 day	2482.6 ± 36.9	2511.4 ± 37.4	10.47 ± 0.311	252.8 ± 8.79
Paired t test	Est. vs BW; p = 0.030			
>1 day	2850.0 ± 30.8	2818.9 ± 31.2	10.43 ± .264	279.2 ± 7.12
Paired t test	Est. vs BW; p = 0.006			
Unpaired t test to ≤1 day	p < 0.001	p < 0.001	p = 0.896	p = 0.027
Equation 5 (n = 1684)				
≤7 days	2703.8 ± 24.0	2686.5 ± 22.8	9.47 ± 0.179	246.4 ± 5.07
Paired t tests	Est. vs BW; p = 0.051			
Paired t test with equation 1	p = 0.007	p < 0.001	p < 0.001	p < 0.001
Prospective evaluation (≤7 days)				
Equation 1 (n = 339)	2713.3 ± 56.1	2696.3 ± 56.3	9.85 ± 0.43	238.9 ± 10.50
Paired t test	Est. vs actual	NS		
Unpaired t test to n = 1684	NS	NS	NS	p = 0.007
Equation 5 (n = 339)	2713.3 ± 56.1	2694.0 ± 54.6	8.77 ± 0.38	219.5 ± 9.7
Paired with equation 1 (prospective)		NS	p < 0.001	p = 0.005
Unpaired comparison to equation 5 (n = 1684) (retrospective)		NS	NS	p = 0.14

Est. vs BW, Comparison of estimated fetal weight to actual birth weight.

tercept of 209 gm (p < 0.0001). This relationship was statistically different from the ideal slope of 1 and an intercept of 0 for ≤1-day, ≤3-day, or ≤7-day examination-to-birth intervals (t = 6.13, 7.87, and 7.25, respectively).

The power analysis indicated there was a 99% probability of detecting a 2% difference between the estimated and actual weights or a difference in the slope of 0.016 for these two variables at an alpha error of p = 0.05. Although a 2% difference in the fetal weights was easily detectable, the probability of detecting a 100 gm absolute difference of an alpha error of 0.05 was 84.8%.[10] A 2% difference in fetal weight is not clinically significant, but a 100 gm difference may be clinically important. This indicated that absolute percent difference may be a more sensitive expression of the differences between the actual and estimated fetal weights over a wide range of weights.

When absolute weight differences were compared by examination-to-birth interval, only the ≤3-day/>3-day pairing had a significantly different distribution (χ^2; p = 0.0093). This observation suggests that the examination-to-birth interval may influence the predictive value of the ultrasonographic estimates. However, both the ≤1-day and ≤3-day intervals had greater percentages of lower weight infants with smaller absolute difference (Figs. 3, *A* and 4) than >1-day and >3-day intervals. This distribution difference can be compensated for by use of absolute percent differences. There was no difference between either of the interval pairings when the difference was expressed as absolute percent difference (Fig. 3, *B*). Furthermore, there were significant linear relationships between actual and estimated weights for all examination-to-birth intervals, but there was no statistical difference between these slopes (Table I). This indicates the data can be further analyzed without regard for the examination-to-birth interval if the absolute percent difference and slopes are used in the analysis.

To compare the regression models in the second part of this study, 77 cases were excluded because of unreported femur length. The initial statistical analysis was recalculated (n = 1684) without any appreciable changes in the means, distributions, or significance (Table II). When several serial examinations were deleted for a true cross-sectional study, the statistics from

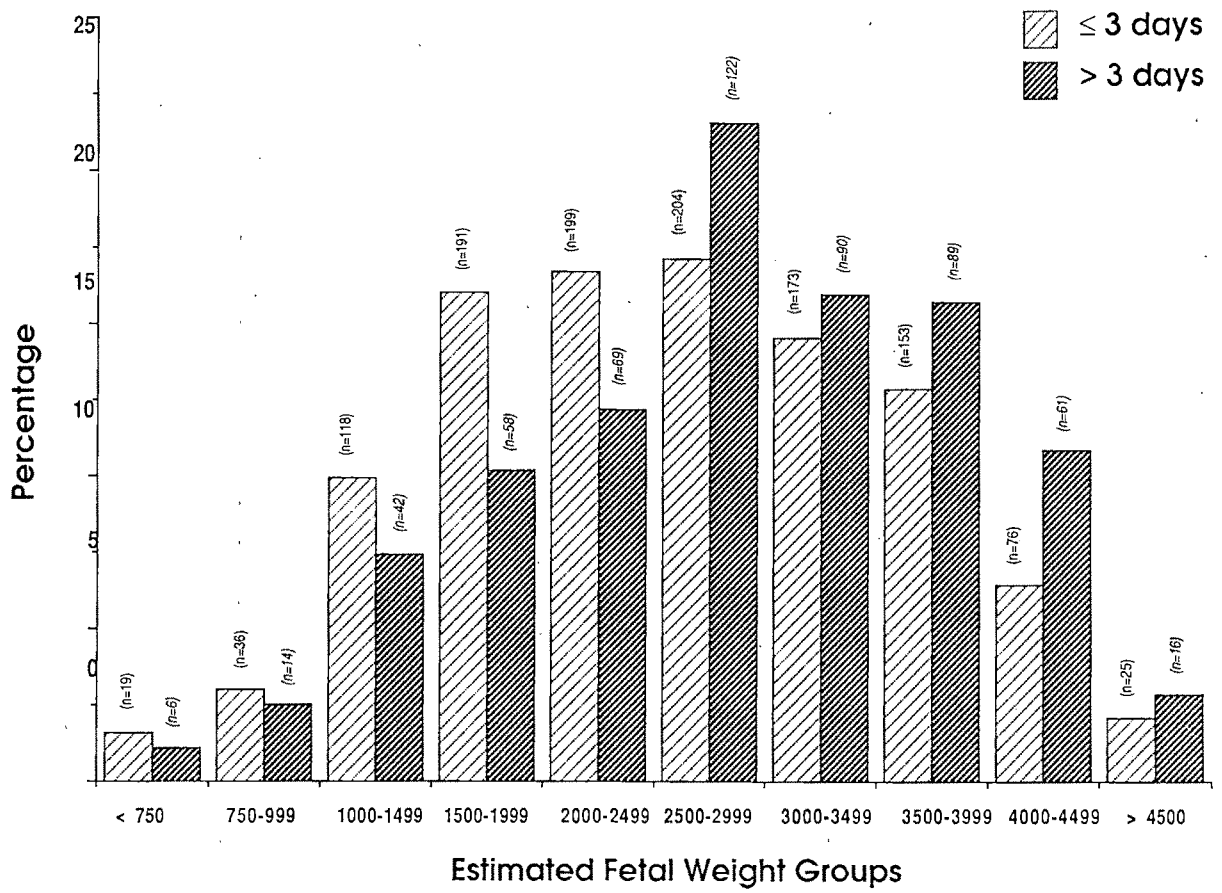


Fig. 4. Population distribution by estimated fetal weight groups. It has been subdivided by examination-to-birth intervals of ≤3 days and >3 days.

the remaining 1560 cases only differed in the third or fourth significant figure from the 1684 cases.

Although many more linear and nonlinear models were constructed, only those that used femur length, BPD, abdominal circumference, and the logarithm of the weight approached an adjusted R^2 value of 0.924. Only for these cases were birth weights regressed against the new estimated weights (Table I). The expected values for the models were calculated to obtain the new estimated weights. A full statistical analysis was performed only on equation 5. It was the model that had a slope closest to 1, a larger R^2 value, and a lower standard error of the slope for the plot of birth weight versus estimated weight than equation 1. More importantly, this new equation was not statistically different from the ideal slope of birth weight against estimate. The improved slope of birth weight against estimated weight was statistically different from the original (equation 1; $p < 0.0001$) or modified Shepard's equations (equation 2; $p < 0.0001$ and $p = 0.014$, respectively).

In comparison with equation 1, the estimates from equation 5 resulted in 5% more (84 additional) fetuses with an absolute percent difference of ≤10%, (χ^2; $p < 0.0001$). The mean absolute percent difference was significantly reduced to 9.46% (paired t test, $p < 0.001$). This new model could detect a difference in distribution of the absolute percent difference between ≤3 days and >3 (χ^2; $p = 0.0107$). This was not possible with the original equation. No significant difference was found when the data were analyzed by ≤1-day or >1-day intervals (χ^2; $p = 0.285$).

The prospective study identified an additional 339 cases with complete ultrasonographic parameters. There were 218 cases delivered within 3 days of an examination, including 147 cases delivered within 1 day. The birth weights ranged from 240 gm to 4885 gm (mean, 2713 ± 56.1 gm). The fetal weights estimated by equation 1, Shepard's original equation, ranged from 283 to 5014 gm (mean, 2696 ± 56.3 gm). The mean absolute percent difference was 9.85% ± 0.43%. Neither the means nor the slope of birth weight against estimated weight from the prospective study were statistically different from equation 1 in the retrospective study.

To confirm whether equation 5 should replace the existing equation, a series of paired and unpaired t tests were performed only on the prospective cases. There

Table III. Prospective: Birth versus estimated weight*

Examination-to-birth	No. of cases	$y = mx + b$		R^2	SE of slope	t Test comparison to ideal	
		Intercept	Slope			t Value	p Value
Equation 1							
≤7	339	144.4	0.953	0.914	0.0159	2.96	0.003
≤3	218	92.2	0.958	0.931	0.0177	2.38	0.023
>3	121	301.4	0.922	0.875	0.0319		
≤1	147	32.1	0.985	0.941	0.0205	0.75	0.45
>1	192	294.4	0.941	0.881	0.0243		
Equation 5							
≤7	339	49.0	0.989	0.925	0.0153	0.72	0.47
≤3	218	27.6	0.984	0.940	0.0170	0.95	0.34
>3	121	127.8	0.983	0.892	0.0314		
≤1	147	−13.1	0.997	0.949	0.0192	0.15	0.80
>1	192	149.3	0.965	0.895	0.0239		

*Comparison with the t test of the regression coefficient. When the slopes of equations 1 and 5 were compared, a t value of 1.638 ($p = 0.10$) was obtained.

were no statistical differences between the estimated weight and the mean birth weight by either equation. The mean absolute percent difference of equation 5, 8.77% ± 0.38%, was significantly lower than equation 1 in the prospective study ($p < 0.001$). The absolute percent difference was consistently not significant in unpaired t tests between the interval pairings. Overall, 5.6% more cases had smaller differences between actual and estimated weights, and 4.8%, or 16 more cases, had an estimate within 10% of actual weight. This result was consistent with the retrospective evaluation.

The differences between the slopes of birth weight against the estimate for equation 5 and equation 1 approached significance ($t = 1.64$, $p = 0.10$). However, when the two equations were compared with the ideal, equation 5 was not significantly different ($t = 0.721$, $p = 0.47$), while the original equation, equation 1, was significantly different from ideal ($t = 2.96$, $p = 0.003$). There was also no difference between the longer and shorter intervals for each equation (Table III). Not surprisingly, for both equations, the shorter interval groups (≤1 and ≤3 days) had slopes and coefficients of determination (R^2) closer to one than their longer interval.

These comparisons of differences and slopes established equation 5 as the best equation for our population. It also established the absolute percent difference as the best comparison of the actual and estimated weights. This finding was consistent with the retrospective evaluation.

Comment

This study evaluated the accuracy of our current ultrasonographic weight estimation equation and developed an equation with statistically lower mean differences of estimated to actual birth weight. This equation has coefficients of regression and determination closer to unity with a smaller intercept than the original equation. An adjusted R^2 value of 0.925 from equation 5 was superior to most of the original work for the "standard" equations.[6-8] This study was initially performed as a large retrospective analysis, confirmed as a true cross-section study with a prospective evaluation of an additional 339 cases. This analysis was made possible because our recording system was an integral part of our ultrasonographic measuring system. Without the integration of the Perinatal Computer Database and the Obstetrical Ultrasound Database, this evaluation would have been difficult.

Although not statistically different in both the retrospective and prospective portions of our study, the shorter examination-to-birth intervals had better linear comparisons and lower differences between actual and estimated weights. For most equations the shortest examination-to-birth interval (≤1 day) had a slope and intercept closest to ideal, followed by the group with an interval ≤3 days. Based on the comparison of the slopes and intercepts of birth weight against the estimated weight, there may be an optimal examination-to-birth interval. When the population was divided by cases delivered within 3 days or more than 3 days, there was a significant difference in the absolute percent difference distribution in the retrospective evaluation, but when the population was reclassified by those that delivered within 1 day or more than 1 day there was no significant difference. The loss of significance when the population was divided by intervals ≤1 day or >1 day may be due to those cases that were born 2 and 3 days after an examination, and whose estimate may be equally accurate, being reclassified into the longer interval group. In addition, in both portions of the study and for both equations 1 and 5, the slope of the ≤3-day interval groups were mirror images of the total population but with lower intercepts. This study indi-

cates than an examination-to-birth interval of less than or equal to 3 days may be optimal.

This study raises several questions concerning ultrasonographic fetal weight estimation. The first question regards the best method to present differences between the estimated and actual weights. The use of actual weight or percentage differences is unsatisfactory because overestimations and underestimations cancel each other. The use of absolute weight differences in grams is only marginally satisfactory as a clinical tool. A 150 gm difference for a 3000 gm infant is a much smaller relative difference than for a 1000 or 500 gm infant. The absolute percent difference remains as the only term that makes clinical sense. It can be uniformly used with all weights.

The next question is which weight should be used as the denominator to calculate absolute percent difference. Previous authors have used the actual birth weight as the denominator.[2-17] This may be mathematically correct for a retrospective study but is less useful clinically. The difficulty with use of a percent difference based on actual weight is that it is an unknown until after birth. It is more practical to have an error range for a known number, the estimated weight, than for an unknown, the actual weight. For the absolute percent difference to be clinically relevant, it is necessary to use the prenatally known variable, estimated fetal weight, as the denominator.

The third question of ultrasonographic weight estimation concerns the weight equation itself. Although our initial equation gave a slope of birth weight against estimate within the range of the existing papers (0.914 to 1.0061),[11-13] it was statistically different from the ideal relationship. The same combination of variables in the original Shepard's equation (equation 1) were entered separately into a multiple regression model; this resulted in equation 2 with completely different coefficients for the variables than the original Shepard equation. This makes at least three forms of Shepard's equation, all with different coefficients for the same variables and each derived from different populations (New Haven, Dallas, and Rochester[13]), that yield inferior weight estimates compared with our best equation, equation 5. It appears that regional population differences may account for the number of studies that expound on finding a "new" ultrasonographic weight estimation equation.[14-17] It is probable that each obstetric ultrasonography laboratory must develop its own estimation equation.[9]

The final question of fetal weight estimation addresses the concerns of previous authors about the need for separate estimation equations for large and small infants.[5, 11, 18-20] These studies suffer from small numbers of subjects and poor controls. The largest number of small infants is 70 in a study by Sabbagha et al.[18] It is also the only study with normal weight controls, but their weight estimation equation uses the gestational age as one of the terms of the equation.[18] Since gestational age is frequently an ultrasonographic estimation, its use in a weight estimation equation may render their equation less accurate than an equation completely derived from the primary ultrasonographic measurements. Examination of Fig. 2, *B*, gives the impression that our population could be divided into two groups at 2500 gm. When separate multiple regression models were developed for each group, the adjusted R^2 value from equation 5 for the total population, 0.926, remained superior to either of the adjusted R^2 values for the ≤2500 gm model, 0.884, or the >2500 gm model, 0.652. This indicates that our population is best represented by a single weight estimation equation and not separate equations for the different weight ranges.

Overall this study has shown that there is a need for a routine evaluation of the accuracy of a laboratory's ultrasonographic fetal weight estimation. It also indicates that this evaluation cannot stop at mere comparisons of birth weight to estimated weight to obtain an absolute percent difference but must include an evaluation of the laboratory's weight estimation equation at regular intervals. Because each population and each ultrasonographic laboratory is dynamic, this equation may require changes to reflect the changes in the laboratory's personnel and population. Finally, a well-integrated ultrasonographic and delivery database is important for evaluation of this methodology on a regular basis.

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Ultrasonographic assessment of intestinal damage in fetuses with gastroschisis: Is it of clinical value?

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In cases of gastroschisis detected prenatally it has been proposed that ultrasonographic criteria may play an important role in the decision for early delivery. We evaluated five cases of gastroschisis diagnosed before birth and found a correlation between prenatally detected small bowel dilatation and severe intestinal damage. However, from the limited data available these in utero measurements seem to be ineffective as indicators for delivery intervention (1) because not all fetuses with bowel dilatation have postnatal evidence of intestinal damage, (2) because some infants with intestinal damage and a poor postnatal outcome may show no in utero evidence of bowel dilatation, (3) because initial bowel dilatation may occur before a gestational age when lung maturity is achieved, and (4) because, in those cases in which bowel dilatation did correlate with intestinal damage, the bowel was already beyond the point of salvage and the infant required bowel resection. (AM J OBSTET GYNECOL 1990;163:995-8.)

Key words: Fetal gastroschisis, bowel dilatation, ultrasonography

In 1988 Bond et al.[1] published a series of 11 cases of gastroschisis diagnosed before birth and correlated the clinical outcome with the ultrasonographic appearance of the eviscerated bowel. They noted that the prenatal presence of small bowel dilatation[2] and mural thickening correlated with severe intestinal damage and a poor postnatal outcome. They subsequently concluded: "now that reliable sonographic criteria of severe intestinal damage have been defined, the decision to deliver early can be restricted to those fetuses with bowel dilatation and mural thickening." We prospectively evaluated our series of cases of prenatally detected gastroschisis to determine whether this conclusion was justified.

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6/6/22579

Case reports

Case 1. A 19-year-old white woman (gravida 2, para 0, [one elective termination]) was referred after multiple episodes of premature labor. Our initial ultrasonographic examination at approximately 32 weeks' ges-

tation showed the presence of an abdominal wall defect consistent with gastroschisis. Evaluation of the fetal bowel showed normal-appearing bowel. Fetal lung maturity was documented by amniocentesis and the mother underwent an uneventful delivery by cesarean section. A female infant weighing 1870 gm was delivered with Apgar scores of 5 at 1 minute and 7 at 5 minutes. The fetus had a stormy postdelivery course and required multiple surgical procedures and subsequently died after approximately 3 months as a result of complications of the gastroschisis.[5]

Case 2. An 18-year-old white woman (gravida 1, para 0) was first referred for evaluation because of an elevated maternal serum α-fetoprotein. Initial ultrasonographic examination showed a fetus compatible with 18½ weeks' gestation and the presence of gastroschisis. Serial evaluations showed no evidence of fetal bowel distention but did show progressive intrauterine growth retardation. Evaluation at 34½ weeks' gestation showed significant bowel dilatation and delivery was accomplished at 35 weeks' gestation after fetal lung maturity was documented by amniocentesis. A female infant weighing 2019 gm with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively, was delivered by cesarean section. Primary closure of the defect was accomplished without complications and the infant was discharged on the twenty-eighth day of life.

Case 3. A 24-year-old white woman (gravida 3, para 1) was initially referred because of an outside ultrasonogram indicative of a fetal abdominal wall defect. Our initial evaluation at 21 weeks' gestation showed the presence of gastroschisis. Multiple evaluations throughout the pregnancy did not show any evidence of bowel dilatation or mural thickening. Delivery was accomplished by cesarean section at 37 weeks' after documentation of fetal lung maturity by amniocentesis. The infant was male with Apgar scores of 8 and 9 and a birth weight of 2825 gm. The abdominal wall defect was easily closed and the infant had a benign postoperative course and left the hospital on the twenty-second day of life.

Case 4. A 21-year-old white woman (gravida 1, para 0) was initially referred for evaluation because of an outside ultrasonogram that showed a questionable fetal abdominal wall defect. Our initial evaluation showed a fetus compatible with 20 weeks' gestation and the presence of gastroschisis. Ultrasonographic evaluations at 22 weeks' gestation and 25½ weeks' gestation showed normal-appearing fetal bowel. Ultrasonographic evaluation at 28 weeks' gestation showed significant fetal bowel dilatation. A repeat ultrasonogram at 32 weeks' gestation again showed fetal bowel thickening in at least one segment. At 34⅓ weeks' gestation there was an increase in the fetal bowel dilatation but fetal lung maturity testing did not show maturity. At approximately 36 weeks' gestation, the mother complained of decreased fetal movement and the fetal heart rate tracing showed the presence of apparent late decelerations. An amniocentesis documented fetal lung maturity and the infant was delivered by cesarean section. A female infant weighing 1880 gm with Apgar scores of 3 and 8 was delivered without complications. A primary closure of the infant's defect was accomplished after resection of a portion of the fetal bowel. The infant had feeding problems and was discharged home on the fifty-eighth day of life while treated by hyperalimentation.

Case 5. A 17-year-old white woman (gravida 1, para 0) was initially referred for ultrasonographic evaluation because of an elevated maternal serum α-fetoprotein level. Our initial evaluation showed a fetus at approximately 17½ weeks' gestation with gastroschisis. Follow-up ultrasonographic evaluations at 22, 25, 28, and 32 weeks showed no evidence of fetal bowel dilatation or mural thickening. There was a decline in fetal growth so that by the time the gestation was 32 weeks by last menstrual period and early ultrasonographic scan, the fetus had measurements consistent with only 28½ weeks' gestation. The patient was again evaluated at 34 weeks' gestation and at that time there was significant dilatation of several loops of fetal bowel. Fetal lung maturity was documented by amniocentesis and the patient subsequently underwent an elective cesarean section. A male infant weighing 1600 gm with Apgar scores of 5 and 7 was delivered. A primary closure of the defect was not possible, and a silo was created. At the time of reoperation there was evidence of necrotic bowel necessitating a bowel resection. The infant had a stormy neonatal course caused by complications of the gastroschisis and bowel resection and was hospitalized for >60 days.

Comment

We evaluated five cases of gastroschisis diagnosed before birth and correlated the clinical outcome with the ultrasonographic appearance of the eviscerated bowel. Three of the five fetuses had in utero evidence of bowel compromise as evidenced by bowel dilatation and increased mural thickness (Table I). Two of these infants subsequently underwent bowel resections and had extremely stormy postnatal courses. One of the infants with in utero bowel dilatation had a primary closure and a relatively benign postoperative course. Conversely, the only infant who died had no evidence of in utero bowel compromise detected by ultrasonographic evaluation. In our experience evaluation of bowel wall thickness did not prove useful. Although there was a tendency for mural thickness to increase with overall bowel dilatation, dilatation was more easily measured and had a better correlation.

Thus we agree with the data presented by Bond et al.[1] that the presence of prenatal small bowel dilatation and mural thickening correlates with severe intestinal damage and a poor postnatal outcome. However, we believe their conclusion that "the decision to deliver early can be restricted to those fetuses with bowel dilatation and mural thickening" is unjustified

Table I. Outcome data for cases of prenatally diagnosed gastroschisis

Case No.	Maternal serum α-fetoprotein (MOM)	Ultrasonography		Gestational age at birth (wk)	Birth weight (gm)	LOS	Outcome
		Gestational age (wk)	MLD (mm)				
1	None	28*	6	33	1870	>90	Died
		32	9				
		32.5	8				
2	7.5	18.5	4	35	2019	28	Good
		23.5					
		27.5	4				
		30.5	5				
		34.5	15				
3	9.6	21.3	4	37	2825	22	Good
		25.3	4				
		29.3	5				
		31.8	5				
		34.3	8				
4	2.3	20.5	2	36	1880	58	Poor
		22	4				
		25.5	5				
		27.7	18				
		32	11				
		34.5	26				
5	4.9	16.6*	4	34	1600	>60	Poor
		17.5	6				
		22	4				
		25	8				
		28.5	8				
		32	8				
		34	16				

MLD, Maximal luminal dimension of the bowel (<10 mm was considered normal); *LOS,* length of initial hospital stay (days); *MOM,* multiples of the median.

*Examinations performed at outside facility; films reviewed.

on the basis of the available data.[4-8] From the limited data available these in utero measurements seem to be ineffective as indicators for delivery intervention for the following reasons. (1) Not all fetuses with bowel dilatation have postnatal evidence of intestinal damage. (2) Some infants with intestinal damage and a poor postnatal outcome may show no in utero evidence of bowel dilatation. (3) Initial bowel dilatation may occur before a gestational age when lung maturity is achieved. (4) In those cases in which bowel dilatation did correlate with intestinal damage, the bowel was already past the point of salvage and the infant needed a bowel resection. Therefore, until more data are accumulated, we believe the delivery of infants with gastroschisis should be based on documentation of fetal lung maturity or other evidence of fetal compromise (such as nonstress testing and contraction stress testing) rather than evidence of bowel compromise. Because bowel dilatation can occur late in gestation, the data may lend some support to the concept of more frequent ultrasonographic evaluation late in gestation or early delivery once lung maturity is documented.

These data also reiterate that even early delivery by cesarean section before labor does not guarantee a benign neonatal course.[9] Although it is unlikely that the actual physical mode of delivery changes the neonatal outcome, there still appears to be the need for a more thorough evaluation of the concept of preterm delivery to prevent the late development of bowel dilatation and the avoidance of bowel compromise as a result of labor (either with or without ruptured membranes). Until more data become available, we discuss the available literature with our patients and allow them to participate in the decision regarding mode of delivery. To date, most patients have chosen cesarean delivery.

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Lack of specific placental abnormality associated with cocaine use

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Detailed gross and histologic examinations were performed on 13 placentas from pregnancies complicated by maternal cocaine use. There were no characteristic changes in placental morphologic features that would explain the increased morbidity associated with cocaine use. It is likely that cocaine exerts its deleterious effects through acute or chronic pathophysiologic changes rather than alterations in placental architecture. (Am J Obstet Gynecol 1990;163:998-9.)

Key words: Pregnancy, placenta, cocaine abuse

Cocaine use during pregnancy is associated with a marked increase in perinatal morbidity and mortality. The complications observed include intrauterine growth retardation, abruptio placentae, preterm delivery, preeclampsia, and fetal morphologic abnormalities that include the skeletal and urinary tract.[1-5] Chasnoff et al.[4] have demonstrated an increased incidence of abruptio placentae and alterations in the neonatal behavioral assessment scale even when cocaine use was limited to the first trimester of pregnancy.

Hertig[6] described certain distinctive placental vascular changes of subendothelial lipid-laden macrophages, fibrinoid deposition, and inflammation of arterial walls in placentas from cases of preeclampsia. Similarly, Dixon and Robertson[7] found abnormalities in placental vessels in patients with preeclampsia and chronic hypertension.

Previous studies from our laboratory[8] and others[9] have demonstrated that acute administration of cocaine results in profound uterine vasoconstriction and increases in uterine vascular resistance. The purpose of this study was to determine whether cocaine use during pregnancy might result in any characteristic morphologic changes in the placenta that might explain, in part, the associated pregnancy complications.

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Methods

Patients were seen for labor and delivery care at the University of California, San Diego Medical Center between Jan. 1 and June 30, 1989; those who had not received prenatal care or were considered to be at risk for drug use were screened for illicit drug use. The urine toxicology screen identified multiple drugs and their metabolites including the amphetamine, barbiturate, cocaine, opiate, and phencyclidine classes of drugs.

A detailed history of drug use was obtained from the mother, and the delivery and newborn records were examined. All cases in which mothers reported a history of multidrug use or in which the drug screen was positive for drugs other than cocaine were excluded from the study. Gross and microscopic examinations of the placenta were performed by one of the authors (K. B.). The study cases were compared with a group of nonrandomly selected placentas from deliveries of similar gestational ages, in which cocaine was not used during pregnancy.

Table I. Outcomes of pregnancies complicated by cocaine use

Case no.	*Gestational age (wk)*	*Delivery*	*Birth weight (gm)*	*Complications*	*Placental abnormality*
1	26	C/S	960	PTL, PTD, PIH	None
2	32	Vag.	1500	SGA, PROM, PTD	Chorioamnionitis
3	37	C/S	2021	SGA, PIH, PTD	None
4	39	Vag.	3130	Meconium staining	None
5	39	Vag.	3948	None	None
6	23	Vag.	375	PROM, PTD	Chorioamnionitis
7	30	Vag.	1620	PROM, PTD	Chorioamnionitis
8	37	Vag.	2300	PIH, SGA, PTD	None
9	21	Vag.	365	IUFD, PTD	None
10	37	Vag.	2090	SGA, PROM, PTD	Chorioamnionitis
11	27	Vag.	1180	PROM, PTD	None
12	38	Vag.	2920	Meconium aspiration	None
13	38	C/S	2353	SGA, abruptio placentae	None

C/S, Cesarean section; *Vag.,* normal vaginal delivery; *PTL,* preterm labor; *PTD,* preterm delivery; *PIH,* pregnancy-induced hypertension; *SGA,* small for gestational age; *PROM,* premature rupture of the membranes; *IUFD,* intrauterine fetal death.

Results

During the time period, 13 patients met the inclusion criteria and were included in this study. The characteristics of patients and pregnancy outcomes are displayed in Table I. Among the 13 patients, 9 infants were born preterm (<37 weeks), 5 sustained premature rupture of membranes, 5 had intrauterine growth retardation (<10th percentile birth weight for gestational age), 2 had preeclampsia, and 2 had meconium staining of the amniotic fluid or meconium aspiration syndrome.

No specific gross or microscopic placental changes were observed. Although the placentas from pregnancies complicated by premature rupture of membranes revealed evidence of chorioamnionitis, the findings were not different from those of placentas of pregnancies with premature rupture of the membranes but without cocaine use.

Comment

Chasnoff et al.[4] reported that women who used cocaine only in the first trimester of pregnancy still had an increased incidence of abruptio placentae. They proposed that early cocaine exposure alone might cause an abnormality in the placenta that would explain the increased incidence of premature separation observed later in pregnancy. Our study detailed examination of the placentas of cocaine-using women revealed no specific abnormalities, and this new evidence would not support such speculation.

Although our study focused on gross and morphologic placental examination, we also observed a high pregnancy complication rate, which has been previously reported.[1-5] Moore et al.[8] examined the hemodynamic effects of cocaine exposure on the ovine maternal and fetal circulations. They found a rapid and highly significant increase in both maternal and fetal arterial blood pressure, as well as a marked decrease in uterine blood flow. These changes persisted for 15 minutes after injection into the maternal circulation and were thought to be secondary to inhibition of norepinephrine reuptake at the nerve terminals.[8] Similarly, Woods et al.[9] confirmed these findings. These acute hemodynamic changes brought about by cocaine use are likely to result in acute vasoconstriction in humans.

In this study we were unable to find any specific morphologic alterations in the placenta that could explain the complications associated with cocaine use in pregnancy. These findings, combined with previously reported physiologic alterations, would support the concept that the fetal morbidity associated with cocaine use is a consequence of pathophysiologic changes rather than morphologic ones. The reason why these pathophysiologic changes are not manifested in morphologic changes is completely unknown.

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TRANSACTIONS OF THE FIFTY-SECOND ANNUAL MEETING OF THE SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

Retrospection and prospection

Presidential address

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It is with considerable pride, great appreciation, and some trepidation that I stand here to present this address. I cannot but recognize that you have elected me to a distinguished group of persons that contains names such as "Daddy" Ross, Bayard Carter, Frank Lock, Charles Collins, and many others who, each in his own way, has contributed much to our specialty and to this Association. Quite a tribute to a foreign medical graduate!

I am sure that each president has considered a wide range of subjects for his address before arriving at a final decision. I found myself reflecting on the circumstances that brought me to this side of the Atlantic Ocean to spend half a lifetime in South Florida, with regard to events that have influenced my career and the practice of our specialty over the years and to changes most likely to affect us in the future. The decision was ultimately made after a recent Sunday at Plymouth Church in Coconut Grove when our Minister "Woody" Hasty in his sermon alluded to "the lift of a long look back" and its value in life. The only problem is that some of us are beginning to realize we have a very long way to look back! I would like to share a few of my reflections with you. We are told that history repeats itself and the truth of that statement is surprisingly obvious as we look back.

I had the good fortune to be born into a medical family and to be reared and educated in that small country north of the river Tweed where friendliness and concern for the individual are almost a part of the national character. My first effort in clinical diagnosis at around age 7 years brought me 3 months in a hospital. I complained to my grandfather, a general practitioner, that I did not feel well and had a sore throat and, having taken a look at it, I informed him that my throat was white. Within an hour I had received a full dose of diphtheria antitoxin and was lying flat on my back in the hospital.

Another recollection was of that same white-haired gentleman coming home after making house calls with my father, also a general practitioner, discussing an amazing occurrence. For the first time they had had the opportunity to treat a patient who had pneumonia with "M&B 693" a sulfonamide and the patient had rapidly recovered. Penicillin was not yet available for clinical use. We have indeed come a long way in medicine in a relatively short time span. The seeds of my interest in obstetrics were probably sown in the same manner. My father and grandfather would discuss midwifery problems between themselves and with the local nurse midwife and with the consultants who came from the teaching hospital on domiciliary consultations.

I was fortunate enough to become a medical student at Glasgow University with its long tradition of excellence in medicine. My guess would be that few of you can say that your university celebrated its 500th anniversary while you were a student. I might add that its tradition of excellence in our specialty has continued under the leadership of one of the guests with us today.

The Hunterian Museum at Glasgow University memorializes the major contributions of the brothers John and William Hunter to medical knowledge. More interesting to us perhaps is the work of their contemporary William Smellie to whom I shall refer later. Students at the Royal Infirmary attended lectures in The

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Lister Lecture Theater named in memory of Lord Lister who advanced the principles of antisepsis in surgery. The members of this association should readily recognize the name Munro-Kerr, a former professor of midwifery at Glasgow who pioneered the low transverse incision in the uterus for cesarean section that continues to have a major impact on our current practice.

The emphasis on clinical bedside teaching was strong. Students considered themselves to be on the cutting edge. Cross-sectional anatomy was being taught and ultrasonography was in its infancy, but little did we realize the impact it would have on our practice. We had to establish the diagnosis with clinical acumen and without the sophisticated ultrasonographic equipment available to today's obstetrician.

Ian Donald in Glasgow and Louis Hellman in New York were pioneering techniques of diagnostic ultrasonography that have revolutionized the practice of obstetrics by providing us with access to the fetus in utero. We now have the ability to assess amniotic fluid volume, fetal maturity, growth and normality, lie and presentation, as well as the location and maturity of the placenta. The biophysical profile has been developed to assess fetal well-being with ultrasonography.

As the equipment has become more sophisticated, chorionic villus sampling at 9 to 12 weeks' gestation has become a viable alternative to the standard amniocentesis at 16 weeks' gestation for genetic diagnosis. Periumbilical blood sampling techniques have provided us with direct access to the fetal vascular system for purposes of diagnosis and treatment. The use of ultrasonography has become such an integral component of obstetric and gynecologic practice it should be handled by the obstetrician-gynecologist rather than the radiologist, with high-quality equipment available on the labor delivery unit 24 hours a day for on-the-spot decision making.

Ultrasonography is also playing an increasingly important role in gynecologic practice. Introduction of the vaginal transducer has enhanced its applicability in such areas as in vitro fertilization, diagnosis of ectopic pregnancy, localization and assessment of pelvic masses and of ovaries in postmenopausal women. Its use is being explored in evaluation of urinary incontinence. Whereas more experience with the use of ultrasonography must be provided in residency training, difficult diagnostic and special procedures should be handled by those obstetricians and gynecologists with special expertise in the field. In addition, ultrasonography is being widely used to complement mammography in evaluation of the breast mass.

My interest in midwifery, or obstetrics as we now term it, began early and was further stimulated by exposure as a student and resident to excellent clinicians and to the writings of the man described in a biography by R. W. Johnson: *William Smellie—The Master of British Midwifery.* I was fortunate enough to have obtained a reprint of one of Smellie's publications: *A Sett of Anatomic Tables,* which was originally published in 1754.[1] The accuracy of the illustrations is incredible as is the clarity of the descriptive text. Equally impressive is the frequency with which many of the principles he espoused almost 250 years ago remain applicable in present day practice. If you have never experienced the opportunity to read some of his work your knowledge in the field of our specialty is incomplete.

William Smellie was born in Lanark on the Clydeside, trained in Glasgow as a medical apprentice to Dr. John Gordon, and opened his practice in Lanark in 1720. He became a member of the Faculty or Physicians and Surgeons in Glasgow in 1733 and was eventually granted his MD degree in 1745. He began the practice of obstetrics despite "stern opposition and offensive epithets" by the local midwives. Subsequently, he moved his practice to London where he established a worldwide reputation as a teacher of doctors and midwives, and unequivocally demonstrated the value of training and experience in obstetrics. Smellie was a giant in his own time and has continued to influence obstetric practice up to the present. Even in London, however, he had his opponents including the midwife who described him as "a great horse-godmother of a he-midwife!" I think it is safe to say that whereas some rancor and difference of opinion still exist, we have for the most part a much more collegial relationship with nurse midwives today. Having worked closely with nurse midwives over the past 35 years I remain convinced that obstetricians, family physicians, and nurse midwives will have to cease bickering, stop the petty jealousies, and agree to join forces and work together as a team if we are ever to be able to render obstetric care to all in this country who need it, and to significantly reduce perinatal and infant mortality.

In 1847 another Scot, James Young Simpson,[2] introduced modern anesthesia in obstetrics. Initially he used ether and later in the same year introduced chloroform for the relief of pain in childbirth. He met opposition from physicians (does that sound familiar?), the public, but particularly the Calvinistic clergy who described him as a heretic, blasphemer, and agent of the devil. They dueled with biblical quotations, but he stood his ground and prevailed.

Six years later John Snow administered chloroform to Queen Victoria at the birth of her eighth child, but the editor of the *Lancet* journal opposed publication of the report. *Lancet* finally reported the use of chloroform at a subsequent delivery in 1857, which was tantamount to a seal of approval by the medical establishment. Controversy did not disappear, even 109 years later in the

mid-1950s Pope Pius XII expressed approval of methods to relieve pain during labor and delivery.

Anesthesia became significantly related to the occurrence of maternal mortality, which in time led to the delineation of obstetric anesthesia as a special field with documented training in this field being required for certification by the American Board of Anesthesia. Anesthesiologists in some instances are now limiting their practice to obstetric anesthesia. In consequence we have seen major advances, especially in techniques of regional anesthesia which was introduced only as recently as the 1940s. Caudal and spinal techniques have for the most part given way to epidural analgesia and anesthesia. Over the years complications of anesthesia have unfortunately remained a significant cause of maternal mortality after delivery by cesarean section, hence epidural (or spinal) has become the procedure of choice in as high as 90% of abdominal deliveries. Newer epidural techniques of labor analgesia involve continuous infusion of a weak local anesthetic agent plus a narcotic (fentanyl citrate). This affords less motor block and more continuous pain relief and holds great promise.

Improved postoperative pain relief has been afforded by continuous epidural block; however, use of the patient-controlled analgesia pump is probably a much more practical approach that gives the patient an element of control over her own pain relief. Other than local nerve blocks, less and less anesthesia is now being rendered by the obstetric attendant.

Equally important has been the spread to this country of the philosophy espoused by Grantley Dick-Read in the 1940s with women expressing their desire for a more "natural" birth, if one may use that terminology. While in training I worked in the same obstetric unit as the midwife daughter of Helen Herdman, the physiotherapist who along with Grantley Dick-Read pioneered "childbirth without fear" or as it later came to be know "natural childbirth." Even in the 1950s prenatal classes were being offered and most women had a spontaneous delivery. With this background it was surprising to find on my arrival in Florida that general anesthesia was frequently induced and forceps were applied for a "normal" delivery.

The explanations given to me for this were multiple, but for the most part were not particularly convincing. It took almost 10 years for the winds of change to start as a light breeze and a further 5 to 10 years for more general acceptance, particularly by obstetricians. The positive aspect of the change has been that for the most part women are now much better informed with regard to childbearing. The expectant father can be equally involved throughout pregnancy and participate rather than being assigned to "boil the water" at the time of delivery. The resistance from obstetricians as one looks back is almost characteristic. Perhaps one can be persuaded to believe that we as a group are somewhat egotistical individuals, some of whom were concerned at the concept of loss of control or had genuine concern of conflict and resisted the presence of family members who were often present when births occurred in the home. Hospitals established rules that in retrospect often appeared more for the benefit of the staff than of the patients. It seems strange that hospitals and many in the medical profession after many years have had to reinvent "family-centered childbirth" in the hospital setting. The same hospitals are now actively marketing their ability to provide this type of care. By recruiting the expectant mother they hope to "capture" the rest of the family. Likewise, obstetricians, to a great degree in response to the pressure by their patients, have become more responsive. For much too long physicians and hospitals simply rejected or ignored these requests. The result was an increasing demand for delivery at home. Most American-trained obstetricians have no experience in this area. Those of us who have had the opportunity to conduct deliveries in the home have learned it can be a very fulfilling experience when no complications arise. However, we have experienced at first hand the problems that may arise even with full backup by a well-equipped obstetric flying squad and know that there is a better alternative. It has been clearly demonstrated that a birth center approved by the National Association of Childbearing Centers or delivery in a hospital that provides family-centered childbirth coupled with early discharge if so desired, are certainly safe and preferable alternatives for appropriately selected patients. A similar philosophy appropriately amended can also be used for women in the tertiary care centers. Despite the continued reluctance of many obstetricians, early discharge is increasingly a reality for all our patients mandated by insurance companies, federal programs, and the affordability of care to private patients, especially in the lower- and middle-income groups. It is disappointing that so many obstetricians have had to be dragged along reluctantly instead of responding objectively and positively to the desires of our patients when it was safe to do so. Equally, the reticence to look at changes in practice occurring in the United Kingdom, Europe, and the Antipodes, to evaluate them, and to adopt them on a more timely basis is hard to explain. A classic example is vaginal delivery after cesarean section, which was a regular practice in Glasgow when I came to the United States in 1960.

Infection as a complication of delivery remains our constant companion. Joseph Lister proved that when bacteria were kept away from the operation site, invasive surgery was possible. Oliver Wendell Holmes attributed puerperal sepsis to infection carried by the

attendant and Semmelweiss in Vienna scientifically proved him to be correct. A profound drop in the obstetric death rate occurred when Semmelweiss insisted on preoperative hand washing with soap and water and soaking the hands in chlorinated lime solution. Almost as one might expect he was opposed by his chief, attacked by his contemporaries, and eventually was forced to leave Vienna. Even his book published 10 years later met opposition—a familiar theme in the history of medicine! The problem of surgical infection was approached by Lister from a different direction. He was luckier in that he held a prominent appointment, worked in an intellectual climate, and was able to prevail in the face of criticism.

He observed that intact skin over a fracture usually resulted in healing of the bones without difficulty; however, when the skin was broken infection developed and pus would drain. After witnessing infections at other operations he postulated the presence of "disease dust" in the air. He recognized the relationship of his findings with Pasteur's work and approached the problem by spraying carbolic acid over the surgical site. A procedure that he subsequently reported in *Lancet.*

Needless to say he also met with disinterest and opposition on both sides of the Atlantic. In a historical review Lyons[3] ascribed to Samuel Gross, one of the leading American surgeons of the day, the statement "little if any faith is placed by any enlightened or experienced surgeon on this side of the Atlantic in the so-called carbolic acid treatment of Professor Lister." The main concept of Lister's work that the infection was introduced at the time of the operation had been overlooked. Nonetheless an increasing number of surgeons around the world had recognized the need to avoid wound contamination. Lister had made a major contribution to surgical progress.

Despite the introduction of gowns, masks, and rubber gloves, surgical infection continues to plague us. We have moved from carbolic acid sprays beyond the sulfonamides and penicillin to fourth-generation cephalosporins and other broad-spectrum antibiotics.

A few present day obstetricians and gynecologists (resident physicians in particular) do not appear to have the same fear of or respect for infection as did their predecessors and must be made to recognize that the basics for prevention of infection in the operating room have not changed in that after the surgeon has scrubbed, gowned, and gloved appropriately, the hands should not touch anything outside of the operating field, not even the gown. Meticulous hemostasis remains important as does gentle handling of tissues. The message that antibiotics are no substitute for good surgical technique must continue to be emphatically delivered.

Improved nutrition, the ability to provide parenteral nutrition, and the use of hyperbaric oxygen in a few cases have contributed significantly to survival in serious surgical infections.

The appearance of human immunodeficiency virus infection is having a major effect on today's midwives, obstetricians, and gynecologists who are delivering infants from or operating on these women. Because in many cases the human immunodeficiency virus status is unknown, adherence to good surgical principles, namely avoidance of injury in the operating room and use of universal precautions, must be stressed. We must increase our knowledge of this disease and with compassion continue to care for these unfortunate women.

Significant infections obviously also occur in early and late pregnancy and may be bacterial, viral, or protozoan. Rubella, herpes, and toxoplasmosis infections continue to alarm our patients and acquired immunodeficiency syndrome now complicates an increasingly large number of pregnancies.

In gynecology human papillomavirus and herpes infections are viewed with concern by our patients because of links to malignant disease of the cervix and absence of a specific curative medication. Paul McDonough[4] in a presidential address before this Association discussed the tremendous potential of deoxyribonucleic acid and ribonucleic acid analysis for identification of infecting organisms and determintion of antibiotic sensitivity as well as the effects of this new technology on the whole field of microbiology.

Among other advances that have occurred in recent years, health care of the postmenopausal woman has assumed a much more important role in gynecologic practice including efforts to prevent or minimize the effects of osteoporosis, hypertension, cardiovascular disease, and endocrinopathy. Exercise, weight control, and screening for gynecologic, breast, and bowel cancer should be an integral part of the package.

Great improvements have been made in management of the premature newborn and to a lesser extent in the control of premature labor. In genetics the picture changes almost on a day-to-day basis. New approaches in repair of recurrent genital prolapse, in the field of laser-laparoscopic surgery, and in management of infertility have been rewarding. These few examples serve only to emphasize the astounding advances that have occurred in our field of medicine in the past 25 to 50 years.

Technologic advances, however, appear to have been counterbalanced by an overall weakening in the doctor-patient relationship, increasing distrust of physicians by patients and their families, resentment of charges by physicians that reflect the increasing cost of running an office but are perceived as price gouging. Occurrence of real or perceived unethical conduct or of frank malpractice perpetrated by persons whom the profession apparently fails to discipline also add to the list of

reasons for patient dissatisfaction and adverse criticism by the media.

Personal observations and those of colleagues, as well as opinions expressed by many patients and their relatives, have convinced me that the single major factor that impairs the doctor-patient relationship today is none of the above, it is the failure to listen to our patients. Second is failure to adequately explain the diagnosis and the plan of management so that patients have a realistic expectation of outcome. This is a constantly recurring complaint. One must seriously question whether the art of the practice of medicine and the quality of care are being sacrificed by some colleagues at the altar of the economics of practice. The basis of sound clinical medicine in any of its fields is to obtain a detailed history. To accomplish this one must listen to the information the patient provides, then perform an appropriate physical examination. It becomes particularly important for a specialist in a limited field to avoid "blinker vision" in care of the patient, especially if we are truly to claim that we are primary care physicians for women.

I am disappointed, but have ceased to be surprised, when a patient informs me "I have never had such a detailed examination" or after a rectovaginal examination: "I have never had that done before." We must ask ourselves why is this occurring. Are we in medical schools failing to impart the appropriate information? The proper techniques are being taught, but perhaps they are not always used in large centers with a high patient volume and emphasis may be placed on a short history, similar to that in a busy office. Board rounds or chart rounds plus a visit to the computer for laboratory results has often replaced rounds at the bedside accompanied by the nurse caring for the patient. It may be that we are not sufficiently emphasizing personal patient contact.

We emphasize risk management, but residents receive little training in the economics of practice, including cost containment, and insufficient preparation to obtain maximum use of community resources. It is unfortunately true to state that in some programs residents do not care for private patients and undergo attitudinal reorientation on entering private practice. One of my mentors, Dr. James MacFarlane, affectionately known to the students as "Gentleman Jim" would have his students sit around a bedside and obtain a full history question by question with discussion of the relevance of each question and of a possible diagnosis, next perform a step-by-step appropriate physical examination, and finally discuss which laboratory tests would be of significance and should be ordered. The 2-hour learning experience was as exciting and interesting for the patient as for the student. It was a unique demonstration of the art and practice of medicine by a clinician par excellence, which left an indelible stamp on those fortunate enough to complete a clerkship on his wards.

Numerous excellent candidates are applying, but are we selecting the right persons as medical students and residents? Perhaps too much emphasis is placed on academic and financial ability in comparison to the patience, tolerance, and compassion needed to care for the young, the elderly, the sick and disabled, or of more importance the ability and willingness to communicate with patients from all levels of society.

One might assume that recruitment into obstetrics and gynecology would be difficult because of the malpractice problem. On the contrary, most good programs continue to have a large number of excellent applicants. Increasing numbers of women and minorities are entering our field of practice, but it still remains to be seen what attitudinal changes that will bring.

In the current climate in which we practice, an attitude of caring and concern by the physician and the ability to communicate with the patient and her family have a major effect on individual exposure to the risk of malpractice litigation.

As we stand on the threshold of a new decade, many of the problems that face us involve social rather than purely medical issues. Highlighted among those are teenage pregnancy, low birth weight and infant mortality, acquired immunodeficiency syndrome, substance abuse, domestic violence and child abuse, medical care for the poor and near poor, and care of the elderly, particularly those in whom mental or physical capability has deteriorated to the point they can no longer maintain their independence.

I recently had the privilege of serving on one of the American College of Obstetricians and Gynecologists new standing committees devoted to health care for underserved women. It was an illuminating, challenging, exciting, and somewhat disappointing experience. It was exciting to sit with a group of persons who were recognizing the problem for what it is and trying to deal with it on those terms. The disappointing aspect was that a not inconsiderable segment of college membership has been unwilling to participate for a variety of reasons. The committee recognized that in the search for solutions, government programs remain a critical component in the effort to care for the poor and that coordination between state, federal, and other programs is needed to obtain the maximum benefit. Physicians must become more knowledgeable with regard to health care public policy as well as to the legislative process. The college has prepared and made available a government relations handbook to help membership in this respect. To be successful the political process must be carried down to grass-roots levels.

Maternal complications, low birth weight, and infant

mortality are inexorably linked with lack of prenatal care. Young, single women who are either black or Hispanic are at particular risk in this respect. Cost effectiveness of prenatal care has been clearly demonstrated yet increasingly greater numbers of women are having difficulty obtaining care.

Provider availability has been affected by low reimbursement rates in Medicaid and state programs. The liability crisis has greatly reduced the number of obstetricians and almost eliminated family physician participation in many areas. Many perceive increased risk of a lawsuit if treating the poor; however, data provided to the committee did not offer statistical confirmation of that fact. Obstetricians and gynecologists will find it increasingly difficult to win public and legislative support for changes in remuneration or tort reform in the face of reluctance or even refusal to treat the poor, the pregnant poor, and the elderly.

Although offered as a solution, Medicaid has many disincentives built in for both the patient and the provider. Provision of the documentation demanded of many patients has been very difficult for a variety of reasons including lack of personal records, of know how, and of transportation. They become discouraged and disinterested. Women on presumptive eligibility drop out of the system before delivery, or eligibility is denied after care has started or even after delivery, which does little to promote participation by physicians. Provision of a full choice of family planning services for those families requesting it must be a priority item. Whereas opposed by some persons it is increasingly obvious that education with regard to reproductive physiology and disease transmission must become an integral part of the school curriculum by the time the student reaches puberty. One may debate the moral and religious aspects of such a policy, but delaying it until the senior highschool level makes absolutely no sense. Many of the young women we care for have had one or more children by the time they reach age 15 years. The concept of preconceptional counseling will remain a dream for years to come under the present system.

Medicaid for the younger and Medicare for the older patients plus a variety of local and state programs offer the only source of care for many. Another large group with a serious problem are those persons or families who have limited insurance or may have recently lost insurance because of a job change or can no longer afford the increasingly high premiums. In fact those in the "low middle income group" probably have greater difficulty obtaining health care than do the poor. They face financial disaster when serious illness occurs. In good conscience, can we allow this to continue?

To compound the whole issue it appears that insurance companies with increasing frequency are following the federal example to limit, dispute, and delay reimbursement to the provider or the patient. In addition, denial of applications for insurance has become more common, as has denial of a claim or even cancellation of insurance after a service has been rendered. Inability to obtain insurance is certainly not limited to lower income or poor women. The cost of private insurance is increasingly unaffordable when obtainable. The potential of serious illness or accident to bankrupt a family has never been higher.

Public pressures are again building for a national health system of some kind and it is obvious that the stage is set differently at this juncture in time. Medicare is in place and physicians are under increasing pressure to elect participating status. Medicaid has been and will continue to be expanded. Greater emphasis is being placed on expanding maternal-child health programs. A greater number of physicians are salaried than in the past. In addition to the reimbursement squeeze by the federal government and insurance companies, preferred provider, health maintenance organizations, and other forms of managed care are on the increase. Subtle rationing of care is occurring and will become more obvious.

Last January the *New England Journal of Medicine*[5] in its editorial[5] commented: "Now is the time for our profession to make common cause with the government and with the major private payers in seeking solutions to a pressing social problem that is not going to solve itself." If as reported 35 million Americans have no health coverage, it is impossible to deny that a serious problem exists and that a solution must be found. It is becoming increasingly important that associations such as the South Atlantic and our college insist on being heard in the dialogues surrounding the changes occurring in the health care system. We must avoid the ostrich approach adopted by many physicians in the United Kingdom before 1948 or history will again repeat itself. The problem is not going to disappear and changes in the way we provide care are inevitable. We must actively fight to retain our ability to provide high-quality care, yet extend its availability to all our citizens. We must strive to preserve independent decision making and personal choice for physicians and for patients. However, drastic problems require drastic solutions. Compromise will be needed on all sides. Private physicians will lose some of their independence, rates of remuneration will be held at lower levels and bureaucracy, which we already think is excessive, will increase if the system is not made "user friendly."

A new generation of excellent obstetricians and gynecologists including a higher percentage of women is entering the specialty and their needs and desires for a satisfying career are going to be quite different from ours.

The American College of Obstetricians and Gynecologists in a statement on "Access to Women's Health Care" in the newsletter in December 1988 called for availability of quality health care to meet every woman's need throughout her life, without costly delays or imposition of barriers. It further stated: "The college and its membership are committed to facilitating both access to and quality of women's health care. Fellows should exercise their responsibility to improve the health status of women and their offspring both in the traditional patient-physician relationship and by working within their community and at the state and national levels to assure access to high quality programs meeting the health care needs of all women."

The knowledge to provide such care is available, but is not presently reaching many of the women who need it most, for which we of the medical profession must bear some of the responsibility.

It is my hope that the political mists around health care will begin to clear and that in the 1990s each member of the South Atlantic Association of Obstetricians and Gynecologists will embrace the "access to care" statement and redouble his or her efforts to bring the concept to reality, although, I suspect that delivery will be preceded by a somewhat protracted and complicated labor.

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Invasive carcinoma of the vulva

Changing trends in surgical management

Denis Cavanagh, MD, James V. Fiorica, MD, Mitchel S. Hoffman, MD, William S. Roberts, MD, S. C. Peter Bryson, MD, James P. LaPolla, MD, and Desmond P. J. Barton, MRCOG, FRCS(Ed)

Tampa, Florida

Four hundred fifteen patients who had invasive carcinoma of the vulva were treated with primary surgery from July 1, 1955, through June 30, 1989. Three hundred seventy-six (90%) of the patients had squamous carcinoma. Two hundred fourteen patients (52%) had radical vulvectomy with inguinofemoral lymphadenectomy. Twenty-four patients (6%) underwent radical vulvectomy with pelvic exenteration for advanced disease, and 55 patients (13%) had nonradical operations. The remaining 122 patients (29%) underwent radical vulvectomy, inguinofemoral lymphadenectomy, and pelvic lymphadenectomy. The primary morbidity was associated with lymphedema (8.6%) and groin wound breakdown (54%). No intraoperative deaths occurred among the 415 patients treated surgically, but there were 17 deaths (4%) within 28 days of operation. The absolute 5-year survival rate was 85% in patients with negative inguinofemoral lymph nodes and 39% when these lymph nodes were positive for metastatic carcinoma. The overall absolute 5-year survival rate was 67%. (AM J OBSTET GYNECOL 1990;163:1007-15.)

Key words: Invasive carcinoma of vulva, vulvectomy, inguinofemoral lymphadenectomy

Invasive carcinoma of the vulva is uncommon and accounts for only approximately 0.3% of all female cancer deaths.[1] However, the steady increase in life expectancy has brought carcinoma of the vulva into more importance among gynecologic malignancies. This is especially so in states with a large number of elderly citizens. In the state of Florida two thirds of patients with cancer are over 65 years of age, compared with approximately 50% in the nation as a whole. The 1980 census reported that Florida's population of approximately 10 million included 17.3% elderly, compared with 13% for the nation as a whole. By the year 2000 the percentage of elderly among the population is expected to increase nationwide, and Florida's population is estimated to be 15 million, with an estimated elderly population of 19.3% or almost 3 million people. With this futher increase in the elderly population the number of cancer cases is expected to almost double by the year 2000. Nationwide, it is estimated that carcinoma of the vulva accounts for 3% to 5% of all gynecologic malignancies, but on the Gynecologic Oncology Service at the University of South Florida in 1988, 30 of 304 patients with invasive gynecologic malignancy had carcinoma of the vulva (10%).

Just 40 years ago the absolute 5-year survival rate for carcinoma of the vulva was 15%.[2] However, a significant improvement in survival has occured because of earlier diagnosis and a better understanding of the nature and modes of spread of this disease.[2-15]

In the not too distant past patients with invasive carcinoma of the vulva were routinely treated with radical vulvectomy and bilateral inguinofemoral (groin) and pelvic lymphadenectomy; now this treatment mode has been seriously questioned.[16] Early vulvar carcinoma has been treated without bilateral groin node dissection for over a decade,[13] and exenteration has proved advantageous for prolonged survival in selected patients with advanced disease.[17] A better understanding of the nature of this cancer, especially the acceptance of the facts that the pelvic nodes are rarely primarily involved and that tumor embolization is the main mechanism for lymphatic spread, has led to changes in the basic operation.

These changing trends in the surgical management of invasive carcinoma of the vulva led us to review our experience over the 34-year period from July 1, 1955, through June 30, 1989. One surgeon (D. C.) participated actively in the management of most of these patients, and all were treated at the University of Miami (1955 to 1966), St. Louis University (1966 to 1977), and the University of South Florida in the

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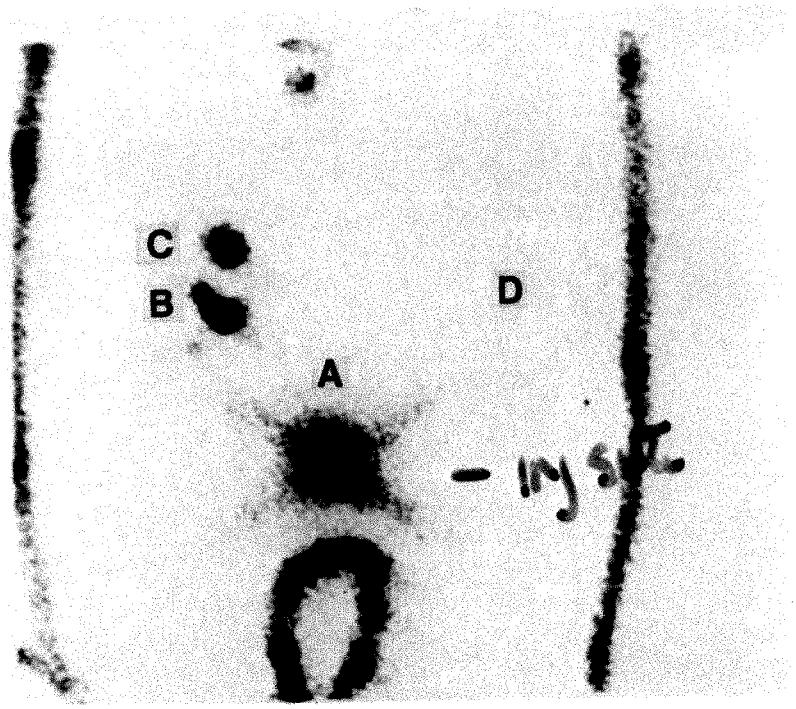


Fig. 1. Lymphoscintigram with technetium intralesionally demonstrates unilateral drainage from a right labial lesion *(A)* to the ipsilateral inguinofemoral *(B)* and external iliac *(C)* lymph nodes. There is no drainage to the left groin nodes *(D)*. Bilateral lymphadenectomy was performed and all nodes were negative for metastatic tumor.

Tampa/St. Petersburg area (1977 to 1989). The therapeutic implications of the findings are discussed.

Patients and methods

Four hundred seventy-six patients were treated for invasive carcinoma of the vulva from July 1, 1955, through June 30, 1989. Of these, 415 patients had primary operation and had adequate data for evaluation. A retrospective analysis was conducted with regard to stage of disease according to the classification of the International Federation of Gynecology and Obstetrics, histopathologic diagnosis, and type of surgical treatment. The main goal of this analysis was to evaluate the effect of these factors on survival and morbidity patterns, and draw conclusions that could improve results in the management of this disease.

Preoperative investigations generally undertaken were as follows: (1) Routine studies included a complete blood count, urinalysis, biochemical profile, serologic testing, blood urea nitrogen, and 2-hour postprandial blood glucose; (2) a Papanicolaou smear was taken of the cervix, and colposcopy of the cervix and vagina was carried out as necessary. The toluidine blue test was used to identify high-risk areas and suspicious lesions were sampled. All outside slides of biopsy specimens were reviewed before operation. (3) Patients were screened for granulomatous disease of the vulva, with special attention recently to typing for the human papilloma virus. (4) Radiologic studies included x-ray films of the chest, intravenous urogram, and barium enema. Recently ultrasonography for liver metastasis and computed axial tomography for the assessment of pelvic and paraaortic lymph nodes have been used. In the past lymphography was routine but now it is only used in carefully selected cases because of the association with lymphangitis. More recently we have used lymphoscintigraphy. This study does not show whether nodes are positive or negative, but the drainage pattern of the lesion can be demonstrated with an intralesional injection of technetium 99 (Fig. 1). (5) Examinations under anesthesia, cystoscopy, and sigmoidoscopy were carried out as indicated. (6) Medical and anesthesiology consultations were obtained before operation.

During the period between 1955 and 1977 the standard operation for invasive carcinoma of the vulva was radical vulvectomy with bilateral inguinofemoral lymphadenectomy and pelvic lymphadenectomy. However, more recently we have discontinued the practice of routine bilateral pelvic lymphadenectomy. Even in patients with clitoral involvement, melanoma, or Bartholin's gland carcinoma, bilateral inguinofemoral lymphadenectomy with radical vulvectomy has become the standard approach.

When possible, two surgical teams were used to de-

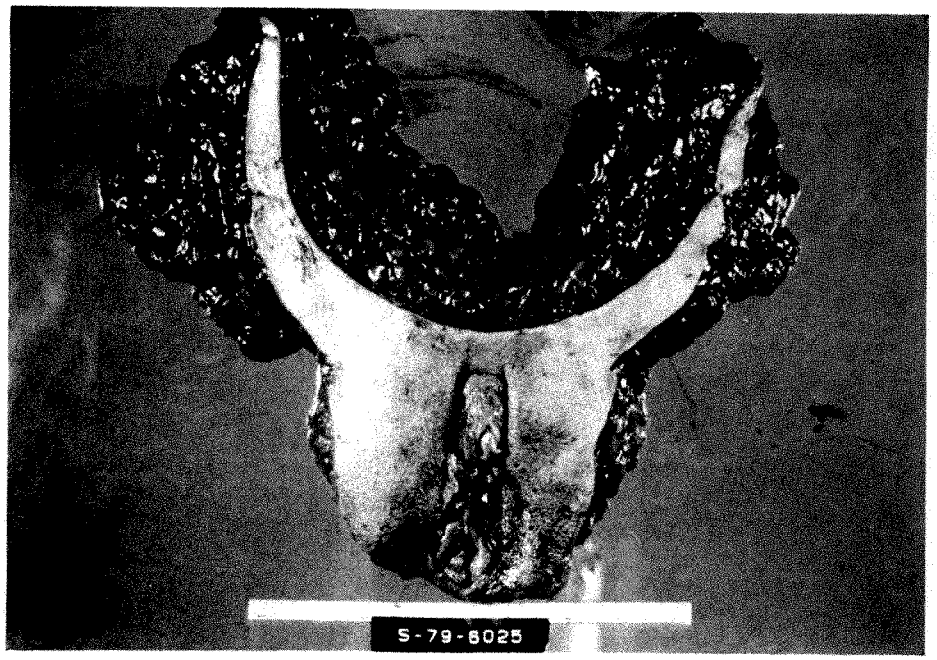


Fig. 2. Radical vulvectomy specimen with vulva removed in continuity with the inguinofemoral lymph nodes.

crease operating time. The procedure was begun with simultaneous bilateral inguinofemoral lymphadenectomy, and then proceeded to bilateral extraperitoneal lymphadenectomy, radical vulvectomy, or both. The operating time for the standard operation ranged from 90 to 270 minutes, with a mean of 150 minutes. With experience the technique has been modified over the years. During the early years an interspinous incision was made, the flaps were undercut, and the groin nodes removed. This resulted in wound breakdown in 90% of patients and therefore the technique was changed. For many years a "winged" incision was made to remove the skin over the inguinal nodes. The tips of the "wings" rested on the anterior superior iliac spines with the upper part of the incision being interspinous in location, and the lower part extending along the inguinal skin creases and into the labiocrural folds to clear all lesions by at least 2 cm. Removal of the lymph nodes was performed en bloc with the vulvar specimen so that continuity of the labiocrural lymphatics was maintained (Fig. 2). The mons pubis was removed and special attention was paid if the clitoris was involved. Dissection was carried down to the fascia so that all tissues were removed superficial to the urogenital diaphragm. Resection of the vagina, urethra, anus, or even bone was performed if the tumor involved these sites. In most patients a covering was placed over the femoral vessels by bilateral transposition of the sartorius muscles. More recently dura mater grafts have been used (Fig. 3).

In 1981 a significant modification in surgical technique occurred. This was based on the fact that lymphatic spread is primarily by embolization and that arrest of significant numbers of cancer cells in the labiocrural lymphatics is very unlikely. Three separate incisions are now used: one incision over each groin and the third is the vulvectomy incision. The groin incisions extended from the anterior superior iliac spine to the pubic tubercle bilaterally, with an elliptical portion of skin approximately 3 cm in maximum width removed from each groin together with the inguinofemoral lymph nodes. This technique leaves a small skin bridge between each area of groin node dissection and the vulva, thus allowing increased vascularity and better wound healing. These groin wounds are closed with no. 2 polypropylene retention sutures and staples. They are drained with Jackson-Pratt drains on low suction. The sutures and staples are left in position for at least 3 weeks (Fig. 4) and are removed in the outpatient clinic. Showers twice daily using a "shower-head" are allowed after 1 week to keep the groin and vulvar areas clean.

Postoperative follow-up has consisted of follow-up every 2 to 3 months for the first 2 years and thereafter at longer intervals, but not exceeding 6 months unless the patient was lost to follow-up. Specimens for vaginal cytologic examination were obtained at each visit. Chest radiographs, and more recently mammograms, have been obtained at yearly intervals with other investigations such as computed axial tomography, ultrasonography, bone scans, or magnetic resonance imaging studies only as indicated.

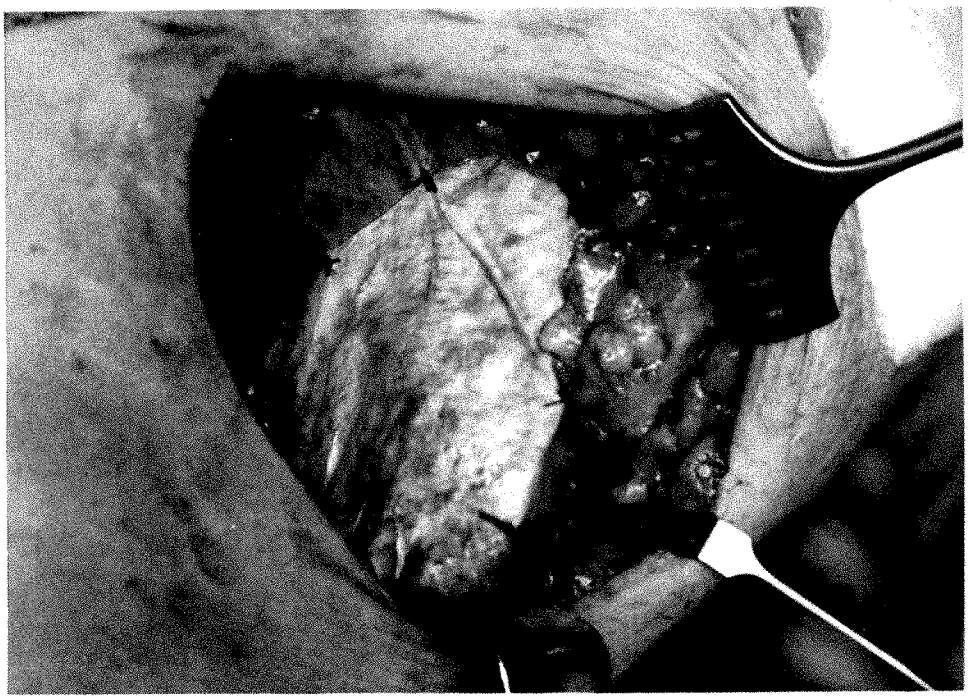


Fig. 3. Dura mater allograft sutured over femoral vessels with interrupted 2-0 polyglactin sutures.

Table I. Invasive carcinoma of the vulva (1955-1989)—Distribution by clinical stage of disease

Stage	*No. of patients*
I	179 (43%)
II	99 (24%)
III	101 (24%)
IV	36 (9%)
TOTAL	415

Table II. Invasive carcinoma of the vulva (1955-1989)—Distribution by histopathologic type

Histopathologic type	*No. of patients*
Squamous carcinoma	376 (90%)
Adenocarcinoma	20 (5%)
Melanoma	19 (5%)
TOTAL	415

Results

Clinical picture. The ages of the patients ranged from 24 to 92 years (median age, 67 years). On review of the epidemiologic profile of these patients, the high-risk patient in our study was typically white, nulliparous, and weighed 70 kg. Pruritus vulvae was the main complaint in over 70% of the patients. Other notable coexistent problems were diabetes (12%), invasive cervical carcinoma (4%), and other cancers (3%). Two of the patients were pregnant when the diagnosis of carcinoma of the vulva was made.

Clinical stage. The clinical stage of the disease was assigned (Table I) in accordance with the International Federation of Gynaecology and Obstetrics Classification that was in effect until 1988, because the original data were not available to allow accurate staging according to the new surgical system. Thus some patients who had perineal involvement and were classified as having stage III disease would currently be classified as stage I or stage II, whereas some of the patients with stage I and stage II disease who had positive nodes would currently be classified as having stage III or stage IV disease.

Histopathologic results. The histopathologic distribution of the lesions is listed in Table II; 90% of the carcinomas of the vulva were of squamous cell type.

Types of surgical treatment. The types of surgical treatment are listed in Table III. All patients were treated according to the stage of disease rather than the histopathologic type of the lesion. The general state of health of the patient was also considered in the decision on the type of surgical treatment to be performed. Twenty-four of 415 patients (6%) underwent ultraradical procedures for advanced local disease. Of these, 18 patients had an anterior or posterior exenteration and six patients had a total pelvic exenteration. The general

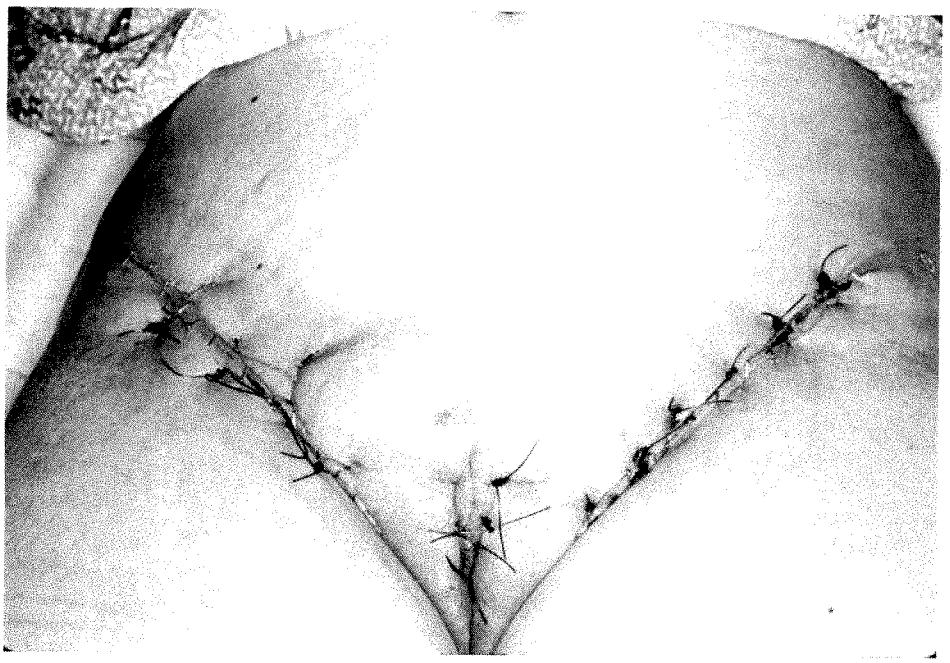


Fig. 4. Three-incision approach to radical vulvectomy and bilateral inguinofemoral node dissection, with closure using No. 2 polypropylene retention sutures and skin staples.

state of health correlated well with the age of the patients; whereas the median age at treatment was 67 years for the whole group, it was 44 years in the patients who had exenteration.

Mortality and morbidity. Although no intraoperative deaths occurred, 17 of the 415 patients (4%) died within 28 days of operation. Ten died of pulmonary embolism and four of myocardial infarction. One died of postoperative hemorrhage associated with pelvic lymphadenectomy. Postoperative osteomyelitis of the pubis with septic shock was the cause of death in one patient. In one patient the cause of death was unknown.

The morbidity pattern assessed in 360 patients is shown in Table IV. Groin wound breakdown occurred in 195 of 360 patients (54%). This was the primary cause of morbidity but was not difficult to treat. The wounds were irrigated with 50% hydrogen peroxide in saline solution three times daily and packed with honey-soaked dressings.[18] Skin grafting was necessary in only two patients. A femoral artery ruptured after operation in three patients and a femoral vein ruptured in two cases, but this complication was eliminated with the use of sartorius muscle transposition or dura mater allografts. Postoperative leg edema was common and persistent lymphedema was a significant problem in 31 of 360 patients (8.6%).

The overall 5-year survival is given by clinical stage of the disease in Table V. Data on 5-year survivals were limited, and no meaningful 10-year survival data were available. Of the 203 patients for whom an uncorrected 5-year survival rate was available, 67% were alive at 5 years. Eighty-six percent were alive if the carcinoma had been diagnosed in stage I, but only 36% of patients with stage IV disease were alive at 5 years. Because of the use of the clinical staging system before 1988, these data should be interpreted with caution when their application to the new surgical staging system is considered.

Table III. Invasive carcinoma of the vulva (1955-1989)—Distribution by surgical treatment

Surgical treatment	*No. of patients*
Radical vulvectomy with bilateral inguinofemoral lymphadenectomy	214 (52%)
Radical vulvectomy with bilateral inguinofemoral and pelvic lymphadenectomy	122 (29%)
Radical vulvectomy with bilateral inguinofemoral and pelvic lymphadenectomy and exenteration	24 (6%)
Total vulvectomy, partial vulvectomy, and other nonradical operations	55 (13%)
TOTAL	415

The absolute 5-year survival rate was 85% for patients with groin lymph nodes that were negative for metastatic carcinoma and 39% with positive groin lymph nodes (Table VI). Patients who survived 24

Table IV. Invasive carcinoma of the vulva (1955-1989)—Postoperative mortality and morbidity

	No. of patients
Mortality (N = 415) (to 28 days)	17 (4%)
Morbidity (N = 360)	
Groin wound breakdown	194 (54%)
Femoral vessel rupture	
Arterial	3 (0.8%)
Venous	2 (0.6%)
Chronic lymphedema	31 (8.6%)

Table V. Carcinoma of the vulva (1955-1984)—Absolute 5-year survival by clinical stage

Stage	*No. of patients*	*Survival*
I	88	76 (86%)
II	59	37 (63%)
III	42	19 (45%)
IV	14	5 (36%)
TOTAL	203	137 (67%)

months after the operation who had positive groin lymph nodes had a 5-year survival rate equal to those with negative lymph nodes. Of 122 patients who had a radical vulvectomy with bilateral groin and pelvic lymphadenectomy, none had positive pelvic nodes with negative groin nodes. Twenty-four of 122 patients (20%) had positive pelvic nodes; only 5 of these (20%) survived 5 years. None of the patients with positive common iliac nodes survived 5 years.

Recurrences—Management and results. A detailed recurrence analysis was performed on 80 patients with carcinoma of the vulva treated between 1977 and 1983. Twenty-three patients were excluded from analysis (7 postoperative deaths, 6 dead of intercurrent disease, 7 treated palliatively, 3 lost to follow-up). Of the 57 eligible patients, 19 (33%) had a recurrence of disease. The sites were vulva (9), groin (1), vulva and groin (1), pelvis (1), abdomen (1), spine (1), lung (3), and undetermined (2). Fourteen of these 19 patients (74%) died of disease. All five patients who survived 5 years had an isolated vulvar recurrence treated with wide local excision.

Perianal lesions—Management and results. From Jan. 1, 1985, through June 30, 1989, a detailed analysis was made of 89 patients who had radical vulvar operation for primary squamous cell carcinoma of the vulva. Thirty-two (36%) of the tumors involved the perianal or anal tissues. Twenty-five patients had stage III disease and seven patients had stage IV disease. Twenty-five of the 32 patients had radical excision of their tumors without colostomy. Two of the 25 excisions included resection of the majority of the anus, and both patients subsequently had severe fecal incontinence. In 12 patients the resection involved partial removal of the external anal sphincter, and persistent postoperative fecal incontinence developed in four of these patients. In the remaining 13 patients the resection involved partial removal of the anal skin, but the external anal sphincter was intact. One of these patients had postoperative fecal incontinence that was unchanged from her preoperative state. Thus carcinoma of the vulva involving perianal tissue can be resected in most cases with adequate preservation of external anal sphincter function. If the sphincter is damaged during operation, there is the potential for subsequent fecal incontinence.[19] In nine patients a portion of the external anal sphincter was excised during operation and the anus was reconstructed with the use of local cutaneous flaps.[20] Bilateral rhomboid flaps were used in seven patients, and two patients had advancement of local full-thickness skin flaps. All nine patients had a satisfactory anatomic result and were ultimately fecally continent. Of the 25 patients who underwent radical perianal excision, one was lost to follow-up, two died of disease at 6 months and 56 months (the two patients who underwent anectomy), and one patient experienced local recurrence at 22 months that was managed successfully with radiotherapy. The mean follow-up period was 23 months (range, 5 to 43 months).

Table VI. Carcinoma of the vulva—Absolute 5-year survival by inguinofemoral node status

Inguinofemoral node status	*No. of patients*	*Survival*
Negative	126	107 (85%)
Positive	77	30 (39%)
TOTAL	203	137 (67%)

Comment

There are ever-changing methods for treatment of carcinoma of the vulva, but radical operations have dramatically improved survival. However, because our aim is to treat the patient and not merely the disease, practitioners must analyze past mistakes and improve patient care. Recently the trend has been toward less radical surgical procedures. Some authors suggest treatment of superficially invasive or "microinvasive" carcinoma of the vulva with wide local excision and ipsilateral and even superficial inguinal lymphadenectomy.[13, 21, 22] One problem with performing superficial inguinal lymphadenectomy is that at least three cases have been reported to have positive deep femoral nodes in the presence of negative superficial nodes.[23-25] An-

other problem is that "microinvasive" carcinoma of the vulva has not been satisfactorily defined. In fact, the Subcommittee on Microinvasive Cancer of the Vulva of the International Society for the Study of Vulvar Disease recommended that the term be abandoned.[26] "Superficial invasion" is a better term, and much thought has been given to its definition.[27, 28] However, when the term "superficially invasive" was used to describe vulvar cancers up to 5 mm in thickness, Sedlis et al.[29] reported that 57 of 272 patients (21%) had metastasis to one node and 28 of 272 (10.3%) had two or more lymph nodes positive for metastatic disease. To clarify the situation the Gynecologic Oncology Group has designed a prospective study to evaluate the management of early invasive carcinoma by wide excision and ipsilateral groin lymphadenectomy. Currently, conservative approaches merit utilization when poor-risk patients are involved. However, like Sedlis et al.,[29] we are not convinced of the validity of abandoning the standard operation at this time in patients with "superficially invasive" disease up to 5 mm, unless other low-risk criteria such as stage I disease, lateral site of the primary lesion, grade 1 tumor, and no lymph or vascular space permeation are taken into consideration. Obviously most of this information is not available before definitive operation.

Lymphangiography can be used to identify lymph node metastasis, but has a limited application in carcinoma of the vulva because it predisposes the patient to lymphangitis and lymphedema. Lymphoscintigraphy has been used to detect nodal location in breast cancer,[30] and recently we have used it in cases of vulvar carcinoma to identify the drainage pattern for individual lesions. It is too early to assess the value of this diagnostic tool in cancer of the vulva at this time.

In 1986 Homesley et al.,[31] in a randomized study of 114 patients, reported that radiotherapy to the groin nodes and pelvis provided a better survival rate than pelvic lymphadenectomy in patients with two or more positive inguinofemoral lymph nodes. Thus radiotherapy now has a place as an adjunct to radical vulvectomy and bilateral groin lymphadenectomy in selected patients.

In 1989 Thomas et al.[32] reported success with the use of concurrent radiation and chemotherapy in selected patients with vulvar carcinoma. We have used this approach in patients with advanced nonresectable disease, and we believe that currently this approach should be reserved for such cases and patients with combined distal and local recurrences. As we found in our patients, vulvar recurrence can be successfully treated with wide excision, but with distant recurrence the prognosis is very poor.

Despite the above-mentioned "innovative methods" for treatment of invasive carcinoma of the vulva, the standard curative treatment remains radical vulvectomy and bilateral groin lymphadenectomy. This remains the treatment of choice even for patients with melanoma of the vulva,[33] and we treated 19 such patients in this manner. However, in our hands the results are not as good as for squamous carcinoma, and of 10 patients followed up for 5 years in this series only 3 were alive and free of disease. Because all the recurrences were associated with metastatic disease, the performance of bilateral groin dissections in patients with no palpable nodes may not be indicated.

Table VII. Postoperative mortality and 5-year survival of patients with advanced vulvar cancer treated by ultraradical surgery

Author	*No.*	*Postoperative mortality*	*5 yr survival*
Rutledge et al.[7] (1970)	13	0	10
Thornton and Flanagan[39] (1973)	12	1	4
Kaplan and Kaufman[40] (1975)	9	1	4
Krupp et al.[41] (1975)	13	2	3
Benedet et al.[42] (1979)	5	0	1
Adams and Daly[43] (1979)	5	1	3
Phillips et al.[44] (1981)	12	1	5
Cavanagh and Shepherd[17] (1982)—updated	13	1	5
Morley et al.[45] (1989)	12	0	7
TOTAL	94	7 (7%)	42 (45%)

The absolute 5-year survival rate in our patients was 85% in cases with negative lymph nodes and 39% in patients with positive lymph nodes, for an overall uncorrected 5-year survival rate of 67%. With a median age of 67 years, on the basis of appropriate life-table data, life expectancy without cancer of the vulva, matched for age and sex is approximately 80% for 5 years. Considering the older median age of our patients, our results (from 1955 to 1984) are similar to those obtained by others in recent years.[34]

A prominent problem in our series was delay in diagnosis; one third of the patients had stage III or stage IV disease at diagnosis. Many of the patients we studied should have undergone a biopsy procedure sooner, and there was apparent need for physician and patient education.

Groin wound breakdown was the main source of postoperative morbidity in the patients studied. As suggested by Hacker et al.,[35] we have used the three-incision approach over the past 8 years. This technique has reduced the groin breakdown rate from 70% to less than 20%. There have been no recurrences in the skin bridge to date in our series, but one case has recently been reported,[36] and thus we will continue to examine our patients every 2 to 3 months for the first

2 years after operation. However, it should be pointed out that the recurrence reported by Schulz and Penalver[36] was associated with a separate vertical groin incision; perhaps the separate oblique groin incisions will afford more protection from recurrence.

Another significant problem with the standard operation is persistent lymphedema of the legs that occurred in nearly 9% of our patients. Because operative treatment of lymphedema is unsatisfactory at this time, management consists of elevation of the legs and the prompt antibiotic treatment of cellulitis. Within 2 years collateral lymphatic pathways usually become established, and the condition may improve if infection is controlled.

Sexual dysfunction is common after radical vulvectomy, and there are few studies on this subject.[7, 37, 38] Although the capacity for intercourse usually remains, patients experience a sense of disfigurement and a reduction in genital sensitivity. Some patients remain orgasmic after vulvectomy, but in one study 70% to 80% reported the end of sexual activity.[7] In evaluating this factor, however, it should be kept in mind that in most series the patients are in the seventh decade of life when they have invasive disease. Modifications in the operation have been proposed to reduce sexual dysfunction, and in recent years we have tried to spare the anterior vulva, mons, and especially the clitoris unless these areas are within 3 cm of the invasive lesion. Dyspareunia and even retention of urine may occur as a result of vaginal stenosis, but this problem is readily treatable by perineotomy and transverse closure of the incision. Skin flaps to replace vulvar tissue are often helpful in enlarging the introitus, and the patient should be encouraged to use a vaginal dilator and resume intercourse after operation.

In our opinion, the preferred mode of treatment for most patients with invasive carcinoma of the vulva is radical vulvectomy and bilateral groin node dissection. There are certain patients who would benefit from alternative therapies, such as bilateral inguinofemoral lymphadenectomy and subtotal vulvectomy with clitoral sparing for posterior lesions.

Exenterations may help patients with locally advanced carcinoma of the vulva, and a recent review of the literature reveals 42 of 94 patients (45%) who survived for 5 years[17, 39-45] (Table VII). However, Boronow et al.[46] have reported good results in the treatment of advanced vulvar disease with initial radiation to reduce or eliminate the need for exenterative surgery. Thus in different centers the approach to the problem of advanced vulvar cancer is handled in different ways, each with a margin of success. The basic problem in evaluation of these treatment methods is that no center has enough advanced cases to conduct a controlled randomized study.

In summary, modifications in surgical technique have reduced the most common complications associated with radical vulvectomy and bilateral groin node dissection. However, because recurrence is the most serious posttreatment problem in patients with cancer, improvement in survival rates is a continuing goal. Earlier diagnosis and prompt referral for appropriate treatment are critical elements for success in this disease, and thus improved patient and professional education is vital.

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Bacterial vaginosis and trichomoniasis vaginitis are risk factors for cuff cellulitis after abdominal hysterectomy

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To assess the relationship between either bacterial vaginosis or trichomoniasis vaginitis and posthysterectomy infection, preoperative evaluation of the vaginal secretions was performed in 161 women undergoing abdominal hysterectomy. Thirty-two patients (19.9%) and 27 patients (16.8%), respectively, met the diagnostic criteria for bacterial vaginosis and trichomoniasis vaginitis. Patients with either bacterial vaginosis or trichomoniasis vaginitis were more likely than control subjects to have cuff cellulitis, cuff abscess, or both (relative risk 3.2, 95% confidence interval 1.5 to 6.7 for bacterial vaginosis; relative risk 3.4, 95% confidence interval 1.6 to 7.1 for trichomoniasis vaginitis). Preoperative vaginitis had no effect with respect to the incidence of postoperative wound infection, urinary tract infection, or intravenous line phlebitis. *Bacteroides* sp., *Peptostreptococcus* sp., and/or *Gardnerella vaginalis* ("bacterial vaginosis organisms") were isolated from the vaginal cuff in the majority of patients with postoperative cuff cellulitis. Bacterial vaginosis and trichomoniasis vaginitis are risk factors for the development of posthysterectomy cuff cellulitis. (AM J OBSTET GYNECOL 1990;163:1016-23.)

Key words: Bacterial vaginosis, trichomoniasis, cuff cellulitis

Pelvic cellulitis remains the most common serious infectious complication after abdominal hysterectomy.[1] Postoperative cuff cellulitis, pelvic abscess, or both occur in up to 18% of women not receiving antibiotic prophylaxis.[2] The pathogenesis of this infection involves the invasion of spaces superior and lateral to the vaginal cuff, including the parametrial tissue, by endogenous microorganisms found in the vagina.

Bacterial vaginosis is associated with an alteration of vaginal bacterial flora as evidenced by a significant increase in the concentration of *Gardnerella vaginalis* and anaerobes in the vaginal fluid.[3] Patients with vaginal trichomoniasis have similar changes in vaginal flora.[4] Several investigators[5, 6] have demonstrated that potentially pathogenic bacteria persist in the vagina despite the use of a povidone-iodine preparation. Infection after surgical entry into the vagina during abdominal hysterectomy is a direct result of the residual bacterial inoculum in the vagina. It follows that those disorders associated with increased concentrations of vaginal microorganisms, such as bacterial vaginosis and vaginal trichomoniasis, may increase the risk of postoperative cuff cellulitis and possibly wound infection. We designed the following prospective study to address this issue.

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Material and methods

Study population. From April 15, 1987, through Jan. 15, 1989, a total of 161 consecutive qualifying patients undergoing abdominal hysterectomy on the Gynecology Service at the Medical College of Virginia Hospitals were included in the study. The study was approved by the Committee for the Conduct of Human Research and each subject gave consent. Patients were excluded if they had received antibiotics within the preceding 2 weeks or if they required cardiac antibiotic prophylaxis. Also excluded were patients undergoing hysterectomy on the Gynecologic Oncology service or patients who had their hysterectomies performed by or under the supervision of gynecologists other than the three coauthors of this article. All operations were performed by gynecologic residents with the assistance of one of the three coauthors.

None of the patients in the study received antibiotic prophylaxis. No preoperative douching was performed. Preoperative vaginal, perineal, and abdominal scrub with povidone-iodine was used in all patients. The surgical technique was standardized. No drains were used with the exception of a subfascial Jackson-Pratt drain in patients having a Maylard incision. The vaginal cuff was closed in all patients. A Foley catheter was left in place until the morning of the first postoperative day.

Clinical evaluation. Immediately before the operation, after the induction of anesthesia but before the vaginal scrub, the vagina was evaluated by one of the coauthors. The consistency of the vaginal secretions was recorded and a pH was determined with colorpHast indicator sticks (MC/B Manufacturing Chemists, Inc.,

Cincinnati) with a range from 4 to 6.5. The lateral vaginal walls were swabbed with a cotton-tipped applicator, which was mixed with two drops of physiologic saline solution on a glass slide. A second slide was prepared with 10% potassium hydroxide and was immediately evaluated for the presence of a fishy aminelike odor (whiff test). Both slides were entirely examined at ×400 with a light microscope. Clue cells were identified as vaginal epithelial cells with such a heavy coating of bacteria that the peripheral borders were obscured. The percentage of epithelial cells represented as clue cells was calculated after evaluation of a minimum of four representative fields. Trichomonads were identified as motile flagellated organisms slightly larger than white blood cells. The potassium hydroxide wet mount was examined for the presence of hyphae.

Microbiologic studies. Cultures of the endocervix were performed for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Cervical specimens for *N. gonorrhoeae* were inoculated onto Transgrow media (Carr-Scarborough Microbiologicals, Atlanta) and incubated in 5% carbon dioxide at 37° C. Oxidase-positive colonies were presumptively identified as *N. gonorrhoeae* by Gram stain showing gram-negative diplococci. Cervical specimens for *C. trachomatis* were extracted into a sucrose-phosphate-glutamate transport medium. Specimens were then inoculated and centrifuged onto coverslips with cycloheximide-treated McCoy cells in two vials. After incubation in 5% carbon dioxide at 37° C for 48 hours, the coverslips were removed and the cells were fixed in methanol and stained with a fluorescein-conjugated monoclonal antibody (MicroTrak, Syva, Palo Alto). Specimens were reported as positive when one or more fluorescing inclusion bodies were seen. A second pass was performed on the second vial of all negative specimens.

Definitions. A patient met the criteria for the diagnosis of bacterial vaginosis if she had ≥20% clue cells, no motile trichomonads, and two of three of the following criteria: pH ≥ 4.7, homogeneous discharge, and/or positive whiff test. A patient with a positive wet mount of the vaginal secretions for motile trichomonads was considered to have trichomoniasis. Control patients had <20% clue cells and no motile trichomonads on wet mount of the vaginal secretions.

Postoperative infections

Cuff cellulitis. Cuff cellulitis was diagnosed in patients with persistent fever (>100.4° F) on two occasions, excluding the first 48 hours postoperatively, in association with increased vaginal cuff tenderness and induration on bimanual pelvic examination.

Cuff abscess. A cuff abscess was diagnosed in patients with the criteria for cuff cellulitis who also had a palpable fluctuant mass located superior to the vagina. In all cases of cuff abscess, dilation of the cuff led to demonstrable drainage of purulent material.

Abdominal wound infection. A wound infection was diagnosed when a wound drained purulent material or serous fluid from which potential pathogens were recovered when cultured. Tissue induration, warmth, erythema, and increasing tenderness were also present.

Urinary tract infection. A urinary tract infection was diagnosed in patients with urinary symptomatology (i.e., urgency, frequency, and/or dysuria) in whom a catheterized urine culture grew $\geq 10^2$ colonies per milliliter of a single uropathogen. Urinary tract infection was also diagnosed in patients with persistent fever (>48 hours postoperatively) in whom no other source of fever could be found and in whom a catheterized urine culture grew $\geq 10^5$ colonies per milliliter of a single uropathogen.

Statistical analysis. Discrete data were tested for significance by means of the χ^2 test or Fisher's exact test. Continuous data were tested for significance with a two-tailed t test. All p values are based on two-tailed tests with $p < 0.05$ being considered significant. To determine the potential confounding effect of multiple variables, a multiple logistic regression analysis was performed. Variables that could be considered risk factors for infection after hysterectomy were included in both univariate and logistic regression analyses. These variables included the presence of bacterial vaginosis or trichomoniasis vaginitis, age, menopausal status, being a clinic patient, weight, preoperative serum albumin level, preoperative and postoperative hemoglobin levels, estimated blood loss, and operating time. Only those variables in the first regression with p values of <0.20 and age, because of a $p = 0.03$ in the univariate analysis, were included in the final regression model to avoid overparameterization of the model. Continuous variables used in the logistic analyses were median centered.

Results

Patient populations and perioperative data. The demographic characteristics of the study groups are shown in Table I. Only the younger age of the patients in the bacterial vaginosis group was significant when data were compared among the three groups.

The mean weights, preoperative and postoperative hemoglobin levels, serum albumin level, surgical procedure, duration of operation, and estimated blood loss are shown in Table II. There were no significant differences among the three groups when these parameters were compared.

Thirty-two patients (19.9%) met the diagnostic criteria for bacterial vaginosis and 27 patients (16.8%) met the criteria for trichomoniasis vaginitis. Eleven of the 27 patients (40.7%) with trichomoniasis vaginitis had evidence of concurrent bacterial vaginosis as previously defined. For this reason additional analyses were per-

Table I. Demographic data

Characteristic	*Group 1: Control (n = 102)*	*Group 2: Bacterial vaginosis (n = 32)*	*Group 3: Trichomonas vaginitis (n = 27)*
Age (yr)	42.8 ± 11.2*	39.4 ± 5.8*	40.2 ± 9.4
Gravidity (mean ± SD)	3.0 ± 2.3	3.5 ± 1.7	2.4 ± 1.9
Parity (mean ± SD)	2.3 ± 2.0	2.8 ± 1.5	1.9 ± 1.8
Race (No.)			
Black	66 (64.7%)	22 (68.8%)	25 (92.6%)
White	33 (32.4%)	9 (28.1%)	2 (7.4%)
Other	3 (2.9%)	1 (3.1%)	0 (0.0%)
Clinic patient (mean ± SD)	83 (81.4%)	26 (81.2%)	26 (96.3%)

*$p = 0.03$ for group 1 versus group 2; no other significant differences.

Table II. Perioperative data

Characteristic	*Group 1: Control (n = 102)*	*Group 2: Bacterial vaginosis (n = 32)*	*Group 3: Trichomoniasis vaginitis (n = 27)*
Weight (kg)	79.1 ± 20.1	74.6 ± 13.2	82.3 ± 22.5
Preoperative hemoglobin (gm/dl)	12.2 ± 1.6	12.5 ± 1.6	12.1 ± 1.4
Postoperative hemoglobin (gm/dl)	10.0 ± 1.4	10.6 ± 1.7	9.8 ± 1.3
Preoperative serum albumin (gm/dl)	4.2 ± 0.3	4.2 ± 0.3	4.3 ± 0.6
Operation performed (No.)			
Total abdominal hysterectomy-only	32 (31.4%)	10 (31.3%)	5 (18.5%)
Total abdominal hysterectomy and adnexectomy	64 (62.7%)	21 (65.6%)	22 (81.5%)
Total abdominal hysterectomy and retropubic urethropexy	6 (5.9%)	1 (3.1%)	0 (0.0%)
Duration (min)	150.3 ± 54.9	138.8 ± 45.1	152.3 ± 47.0
Estimated blood loss (ml)	448.1 ± 299.6	508.6 ± 374.1	418.0 ± 204.7

formed. Patients with trichomoniasis vaginitis and concurrent bacterial vaginosis were combined with the group with bacterial vaginosis ($n = 43$), and patients with pure trichomoniasis vaginitis without concurrent bacterial vaginosis were separated into another group ($n = 16$). Fungal elements were seen on the potassium hydroxide preparation in only three patients.

A single patient had a positive culture for *Neisseria gonorrhoeae*. This patient was one of the control patients and had an uncomplicated postoperative course. Three patients—one in each group—had a culture that was positive for *Chlamydia trachomatis*. The chlamydia-positive patient in the group with trichomoniasis vaginitis had postoperative cuff cellulitis.

Postoperative outcome. Cuff cellulitis, cuff abscess, or both occurred in 32 of the 161 patients (19.3%). Patients with bacterial vaginosis were more likely to have cuff cellulitis, abscess, or both (relative risk 3.2, 95% confidence interval 1.5 to 6.7) than control patients ($p = 0.005$). The fever index was significantly higher in patients with bacterial vaginosis than in the control patients. Patients with trichomoniasis vaginitis were also more likely than control patients to have cuff cellulitis (relative risk 3.4, 95% confidence interval 1.6 to 7.1; $p = 0.002$) and had a significantly higher fever index. These data are summarized in Table III. In addition, four of six patients with cuff abscesses had preoperative bacterial vaginosis. Although the numbers are small, this difference was significantly different from the control group ($p = 0.03$).

The significant association of bacterial vaginosis with postoperative cuff cellulitis was even more evident when patients with trichomoniasis vaginitis and concurrent bacterial vaginosis were added to the group with bacterial vaginosis (relative risk 3.6, 95% confidence interval 1.8 to 7.1). When the patients with concurrent bacterial vaginosis were excuded from the group with trichomoniasis vaginitis, the number of patients became too small to result in any meaningful conclusion. Patients with pure trichomoniasis vaginitis did show an increased risk for development of cuff cellulitis; however, this risk failed to reach statistical significance (relative risk 2.3, 95% confidence interval 0.8 to 6.4; $p = 0.12$).

No significant differences were noted among groups with respect to the incidence of wound infection, uri-

Table III. Postoperative outcome

Group	*Cuff cellulitis*		*Fever index (F degree hr)*	*Hospital duration (days)*
	N	%		
1 (Control)	11/102	10.8	84.8 ± 60.1	5.4 ± 1.4
2 (BV)	11/32	34.3	129.8 ± 118.0	6.3 ± 3.3
3 (TV)	10/27	37.0	130.1 ± 90.8	6.0 ± 2.5
p Values				
Group 1 vs 2	0.005		0.046	NS
Group 1 vs 3	0.002		0.020	NS
Group 2 vs 3	NS		NS	NS

Table IV. Univariate analysis of potential risk factors for cuff cellulitis

Characteristic	*Cuff cellulitis (n = 32)*	*No cuff cellulitis (n = 129)*	*p*
Age (yr)*	38.2 ± 9.0	42.6 ± 10.2	0.03
Postmenopausal (No.)	1 (3.1%)	13 (10.1%)	NS
Weight (kg)	75.6 ± 13.3	79.5 ± 20.7	NS
Clinic patient (No.)	25 (78.1 %)	110 (85.3 %)	NS
Duration of surgery* (min)	147.4 ± 56.1	148.5 ± 50.8	NS
Serum albumin (gm/dl)*	4.2 ± 0.4	4.2 ± 0.4	NS
Preoperative hemoglobin (gm/dl)*	12.5 ± 1.4	12.2 ± 1.6	NS
Postoperative hemoglobin (gm/dl)*	9.7 ± 1.4	10.1 ± 1.5	NS
Estimated blood loss (ml)*	492.2 ± 316.3	445.9 ± 299.4	NS

*Mean ± SD.

nary tract infection, and intravenous line phlebitis. Bacterial vaginosis, trichomoniasis vaginitis, or both did not predispose to wound infection.

Analysis of risk factors. Only younger age was statistically significant in the univariate analysis of potential risk factors for cuff cellulitis (Table IV). Multiple logistic regression analysis identified three risk factors that were independently and significantly associated with the development of cuff cellulitis. These factors were bacterial vaginosis, trichomoniasis vaginitis, and a lower postoperative hemoglobin level. A higher preoperative hemoglobin level, younger age, and being a private patient all had an effect on the incidence of cuff cellulitis but failed to reach statistical significance (Table V).

All potentially confounding variables used in the logistic regression model were equally distributed among the three groups of patients with the exception of age (patients with bacterial vaginosis were younger than control patients). However, the independent relationship between bacterial vaginosis and cuff cellulitis was stronger ($p = 0.002$) than the relationship between age ($p = 0.08$) and cuff cellulitis (Table V). The number of private patients in the study was small ($n = 26$). This reflects the mix of clinic and private patients seen in the Benign Gynecology Service at the Medical College of Virginia and not the exclusion of private patients from the study. Despite the fact that 78% (25/32) of all cases of cuff cellulitis were diagnosed in clinic patients, 26.9% (7/26) of private patients, compared with 18.5% (25/135) of clinic patients, had cuff cellulitis (p = NS by univariate analysis, χ^2).

Consequences of morbidity. Patients with cuff cellulitis had a significantly longer duration of hospitalization when compared with their noninfected counterparts (8.1 ± 3.2 vs 5.1 ± 1.1 days; $p = 0.0001$). Also the fever index of patients with cuff cellulitis was significantly higher than it was for noninfected patients (207 ± 99.4 vs 75.2 ± 51.1 degree hours; $p = 0.0001$). This increase in the fever index carried over into the groups of patients with either bacterial vaginosis or trichomoniasis vaginitis; there was a significant difference in the fever index between both the groups with bacterial vaginosis and trichomoniasis vaginitis when compared with the control group (Table III).

Microbiology of postoperative infection. Cultures of the vaginal cuff from patients with postoperative cuff cellulitis were available in 29 of 32 patients (90.6%). These cultures reflect the polymicrobial nature of this infection. More than one organism was isolated from 27 of 29 patients (93%). More important, bacterial vaginosis organisms (*G. vaginalis, Bacteroides* sp., or *Peptostreptococcus* sp.) were isolated from 18 of 29 patients (63%).

Table V. Logistic regression analysis of risk factors for the development of postoperative cuff cellulitis

Characteristic	*Estimate*	*Standard error*	χ^2	*p Value*
Bacterial vaginitis	1.6928	0.5372	9.93	0.002
Trichomoniasis vaginitis	1.7859	0.5598	10.18	0.001
Age	−0.0415	0.0237	3.07	0.08
Postoperative hemoglobin	−0.4741	0.1898	6.24	0.01
Preoperative hemoglobin	0.3436	0.1797	3.66	0.056
Clinic patient	−0.8440	0.5683	2.21	0.137

Comment

Risk factors for infection after hysterectomy have only been prospectively studied by Shapiro et al.[7] They found that the duration of the operation, lack of antibiotic prophylaxis, younger age, being a clinic patient, and an abdominal approach were significantly associated with infection at the operative site. All of our patients underwent abdominal hysterectomy and none received antibiotic prophylaxis. Results of our study failed to confirm that the duration of the operation, younger age, and being a clinic patient are significant risk factors for postoperative infection. In our study all surgery was performed in a standardized fashion by residents with direct assistance and supervision by one of the three coauthors. For this reason the duration of the operation may not be an indicator of surgical proficiency when compared with a study in which experienced private physicians are compared with residents in training. Younger age did have an effect on the incidence of cuff cellulitis, but this relationship failed to reach statistical significance (odds ratio 1.0, 95% confidence interval 0.9 to 1.0; $p = 0.08$). Moreover, the risk factors of younger age and being a clinic patient may have been indications of a patient's risk for bacterial vaginosis or trichomoniasis vaginitis rather than any inherent risk of infection. Our data suggest that this was indeed the case. Our analysis actually shows a trend toward the private patient being at increased risk for cuff cellulitis (Table V). This may well be related to the higher incidence of preoperative bacterial vaginosis in our private patients (23.1%) when compared with our clinic patients (19.3%).

Hemsell et al.[2] used a stepwise discriminant analysis to identify three factors (age, absence of excessive uterine bleeding, and absence of an abnormal uterus at bimanual examination) associated with postoperative infection. However, this report neither described the variables that were used in developing the model nor defined the risk factors. No one has previously evaluated the effect of preoperative vaginitis on the incidence of postoperative infection.

A number of infections occurring in women have been found to be associated with bacterial vaginosis. These infections include pelvic inflammatory disease,[5] postpartum endometritis,[8] and intraamniotic infection.[9] In addition, adverse pregnancy outcomes such as premature labor and preterm delivery have also been linked to bacterial vaginosis.[10, 11] In all patients it was thought that the increased concentrations of microorganisms in the vagina that are associated with bacterial vaginosis predisposed patients to an ascending infection.

Our data show that both bacterial vaginosis and trichomoniasis vaginitis are risk factors for the development of postoperative cuff cellulitis. We believe that the increased concentration of anaerobic bacteria, particularly *Bacteroides* sp. and *Peptostreptococcus* sp., in the vaginas of patients with bacterial vaginosis predisposes them to infection. This is supported by the fact that bacterial vaginosis organisms were isolated from the vaginal cuff of more than 60% of our cases of cuff cellulitis. The vaginal flora associated with trichomoniasis vaginitis is similar to that of bacterial vaginosis.[6] Moreover, trichomoniasis vaginitis is commonly associated with bacterial vaginosis. Whether this association is truly a reflection of two separate disorders or the result of the effect of the trichomonads themselves, causing an increase in vaginal pH and therefore enhancing bacterial adherence leading to the formation of clue cells, is unknown. In our study 40.7% (11/27) of patients with motile trichomonads also showed evidence of bacterial vaginosis (≥20% clue cells, pH ≥4.7, and/or a homogeneous discharge or positive whiff test). Additional analyses showed a weaker association between trichomoniasis vaginitis and postoperative cuff cellulitis when patients with concomitant bacterial vaginosis were excluded. However, it is important to consider trichomoniasis vaginitis as a risk factor for postoperative infection because of its association with bacterial vaginosis and because it is sometimes more easily recognized and diagnosed than bacterial vaginosis.

Logistic regression analysis also identified a lower postoperative hemoglobin level as a risk factor for cuff cellulitis. Univariate analysis of patients with and without cuff cellulitis, as well as analysis among study groups, failed to confirm this significance. Estimated blood loss was not a risk factor for infection. Low postoperative hemoglobin levels may be an indication of postoperative oozing and the resulting subclinical hematoma formation at the operative site, which may pre-

dispose to infection. However, only two of our patients with postoperative cuff cellulitis had clinical evidence of a postoperative hematoma. The statistical significance may not be clinically relevant in this instance.

Preventive strategies have primarily embraced the use of prophylactic antibiotics with variable preventive effects.[1,2] In our study more than two thirds of the cuff cellulitis occurring in the groups with vaginitis could be attributed to bacterial vaginosis, trichomoniasis vaginitis, or both (attributable risk 68.6% and 70.8%, respectively). Future studies should address the effectiveness of preoperative therapy of bacterial vaginosis and trichomoniasis vaginitis with regard to subsequent infection rates. In addition, the effect of perioperative prophylactic antibiotics with respect to risk reduction in patients with bacterial vaginosis or trichomoniasis vaginitis should also be assessed.

The morbidity associated with major postoperative infection is significant. In this study patients with postoperative cuff cellulitis remained in the hospital an average of 3 days longer than patients without the infection. Also the mean fever index of infected patients was more than double that of the uninfected patients. These data clearly support our contention that bacterial vaginosis and trichomoniasis vaginitis do not just predispose to "febrile morbidity" but to clearly diagnosed pelvic infection. Indeed 18.7% (6/32) of patients with cuff cellulitis had clear-cut cuff abscesses.

In summary, we have performed a prospective study to determine the effect of preoperative vaginitis on postoperative infectious morbidity after hysterectomy. Bacterial vaginosis and trichomoniasis vaginitis are risk factors for postoperative cuff cellulitis. Further study is needed to determine what modulating effects either preoperative therapy or perioperative prophylactic antibiotics have on these risk factors.

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Editors' note. This manuscript was revised after these discussions were presented.

Discussion

DR. BERTRAM C. FINCH III, Charleston, South Carolina (Official Guest). The entity bacterial vaginosis has gotten much attention recently. After World War II, results of the first meaningful studies on "nonspecific" vaginitis were reported. In October 1954, Gardner and Dukes[1] incriminated a gram-negative pleomorphic rod as the single causative agent in the infection; they assigned the newly isolated bacillus the name *Haemophilus vaginalis.*[1] This organism has now been reclassified as the only member of a new genus, *Gardnerella.*[2]

G. vaginalis is found in 95% of symptomatic women with bacterial vaginosis and in concentrations 100-fold those of asymptomatic women with no signs of vaginitis or vaginosis. Nonetheless, the organism is found in the normal vaginal pool of up to 40% of asymptomatic women. Compared with these asymptomatic women, those with bacterial vaginosis also have a dramatic 1000-fold increase in total anaerobic bacteria.[3]

Bacterial vaginosis, defined by the same criteria as presented by Dr. Soper, has been recognized in more asymptomatic than symptomatic women. Bacterial vaginosis is said to be the cause of one third to one half of all infectious vaginal conditions and is symptomatically present in 12% to 19% of gynecologic patients.[3] In the past decade bacterial vaginosis has been significantly related to an array of obstetric and gynecologic morbidity; included in the list are premature labor,[4] premature rupture of the fetal membranes,[5] premature birth,[6] postpartum endometritis,[7] chorioamnionitis,[8] infection of the amniotic fluid,[4] pelvic inflammatory disease,[8] and now posthysterectomy cuff cellulitis and formation of cuff abscess.

Three diagnostic methodologies prevail: clinical, microbiologic, and Gram stain. Dr. Soper has used a meaningful clinical diagnosis of bacterial vaginosis that has been used by several authors; according to this definition bacterial vaginosis can be accurately diagnosed when three of four criteria are present. Gram stain appears to be the most sensitive diagnostic method[8]; it can be nonbiased, it lends itself to mass screening, and it allows late and repetitive analyses. Would this test detect other women with bacterial vaginosis who are thus at risk for postoperative morbidity?

Dr. Soper demonstrated that both bacterial vaginosis

and trichomoniasis vaginitis are risk factors for the development of postoperative morbidity, including fever index, prolonged hospitalization, and formation of vaginal cuff abscess. In fact 20% of those with cuff cellulitis also had an abscess. Would this frequent and more serious complication alone account for the increased fever index and prolonged hospitalization?

No intervention strategies were mentioned. Were the 32 women with cuff cellulitis treated with antibiotics? After discharge from the hospital, were any patients readmitted or later found to have conditions requiring antibiotic therapy?

Intraoperatively were any patients found to have pyosalpingitis or chronic pelvic inflammatory conditions that might increase their chances of postoperative fever, tenderness, and/or induration?

Dr. Soper mentioned the persistence of potentially pathogenic bacteria after the use of a povidone-iodine preparation. Indeed Monif et al.[9] showed a dramatic and rapid decrease in the number of aerobic and anaerobic bacteria in the vagina after its use. The effect lasted approximately 1 hour after the solution was used; changing the vehicle to polyethylene glycol (i.e., Betadine vaginal gel) prolonged the effect over a 3-hour period. Since these hysterectomies varied in length from just over 1 1/2 hours to just under 3 1/2 hours, averaging less than 2 1/2 hours, we wonder if the addition of Betadine vaginal gel to the "routine preparation" would reduce the postoperative infectious morbidity.

As Dr. Soper has indicated, as such data accrues, the pathophysiologic mechanisms for these associations will lead to appropriate prophylactic measures, preventive measures, or both. This article offers great potential for reducing infectious morbidity and may aid in controlling hospital expenses with a simple preoperative evaluation. As Gardner and Dukes[1] stated, "Perhaps most serious postoperative infections could be avoided if pelvic surgeons would perform just two simple tests: vaginal pH and a saline wet mount."

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Dr. Guy I. Benrubi, Jacksonville, Florida. We are doing Gram stains because we are finding that what even experienced examiners think is bacterial vaginosis on wet preparations turns out not to correlate with what we are finding on Gram stain. Another interesting finding is that some people with bacterial vaginosis have *Mobiluncus* and some people with BV have *Gardnerella.* We have been doing some quantitative *Gardnerella* cultures. I wonder if that was considered at all. I also wonder whether *Mobiluncus* and *Gardnerella* play different roles in postoperative cuff cellulitis.

We also performed a study several years ago in which 2 gm of metronidazole was given by mouth the night before. We had a population very similar to that of Dr. Soper; 90% of our patients were from a clinic population. The postoperative infection rate, is 18% why not obtain the data while the patient is asleep and then begin treatment with some preoperative antibiotic that covers anaerobic bacteria. This study needed to be done, and I think we are well on our way in trying to elucidate this problem.

Dr. Karen Kreutner, Charleston, South Carolina. This topic was discussed at a full-day seminar at the annual meeting of the Infectious Disease Society. It is very controversial and there is a lot to be learned about BV. One of the main points is that the definition is not as presented in this article. It is very important that we define our terms according to the national standards, which do not, for example, include >20% clue cells, or we are going to end up with a great deal of confusion in the literature. We do not yet know how to treat bacterial vaginosis. *Mobiluncus* does play a role. *Gardnerella* can be downgraded in a number of patients. The newer methods of therapy seem to involve the use of intravaginal clindamycin. We just need to be careful to follow the standards if we are going to publish data.

Dr. William E. Josey, Atlanta, Georgia. I commend Dr. Soper for including trichomoniasis, because up to now most of the studies on infectious morbidity of this type have emphasized *Gardnerella*-associated vaginitis and have not said much about trichomoniasis. I think this is because the anaerobic overgrowth in both of these infectious vaginitides is very similar.

Dr. Soper (Closing). I too was involved in the Infectious Disease Society symposium, and there is no real gold standard for the diagnosis of bacterial vaginosis. Whether composite clinical criteria are used, which are what we use and which are what most investigators who

have published on the subject would consider the so-called gold standard, or whether bacterial vaginosis is confirmed by Gram stain, the bottom line is an alteration of the vaginal flora that is associated with an increased concentration of potentially pathogenic organisms. Patients with bacterial vaginosis are probably best identified clinically by means of composite clinical criteria, because this can be done in the office without having to wait to do the Gram stain, and many physicians may not do Gram stains in their offices. It seems that in looking at the correlations of Gram stain and composite clinical criteria with the diagnosis or microbiology of BV, it is probably best to use composite clinical criteria when making a diagnosis of bacterial vaginosis.

As far as whether abscess alone accounted for increases in the fever index and hospitalization, we still had an increase in the fever index as compared to people who were not infected, and we probably would not have had such a dramatic increase in hospitalization, but the people who were infected had an average stay of 8 days versus an average stay of 5 days for those who were not infected. There was a single readmission. Some of our previous work addresses the fact that unless patients are followed postoperatively after they have gone home from the hospital, all of the postoperative infectious complications may not be noted. We did not see any further problems except in one patient and that patient was included in the statistics. There were no acute infections or pyosalpinx or problems that we thought would predispose to infection or postoperative infection at the time of the original surgery.

It is interesting that a preparation other than povidone-iodine was mentioned for consideration. Indeed, Hibiclens or similar preparations may actually be better than povidone-iodine for sterilizing the vagina. Studies done on vaginal preparations have noted that there is an immediate decrease in the overall concentrations of bacteria, but by the time 30 minutes has elapsed concentrations have pretty much returned to normal. In an operation lasting a little more than 2 hours, it has not been unreasonable to assume that the flora is thriving almost as well as it was before the vaginal preparation was done.

Regarding Dr. Benrubi's statement about the Gram stain not correlating with clinical findings, I think it depends on what your gold standard is. We are actually in the midst of another study on bacterial vaginosis in which we are looking at Gram stains. The Gram stain can be a nice quality-control measure where if others are making the diagnosis of bacterial vaginosis and there is a so-called expert in this field, he or she can review the Gram stain to make sure that bacterial vaginosis is indeed the diagnosis.

Gardnerella vaginalis and *Mobiluncus* may well play a role in the pathogenesis of infection, and frankly any organism in the vagina, if present in high enough numbers and in a pure culture, can be a pathogen. We did not use perioperative antibiotic prophylaxis because we wanted a very clean study. For this reason we did not use vaginal hysterectomies, because we thought it was important that these patients not be given prophylactic antibiotics.

Cases with ruptured membranes that "reseal"

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Among patients with a diagnosis of preterm prepartal rupture of the membranes, an occasional case ceases to leak amniotic fluid before the onset of labor. The purpose of this case-control study was to determine the characteristics and obstetric outcomes of this unique group of patients. This diagnosis was made in 24 such patients who gave birth in 1984 and 1985 at Shands Hospital. Compared with matched control subjects who continued to leak fluid, there were no significant differences in maternal race, age, marital status, socioeconomic status, smoking status, or past obstetric performance. Amniotic fluid volumes, as assessed by ultrasound studies, were less in the group that failed to "reseal." The "reseal" group had longer durations of pregnancy, larger babies, longer maternal hospitalization, less neonatal hospitalization, and less perinatal mortality and morbidity. The occurrence of "resealing" appears to bode well for the mother and infant. Such cases should be sought aggressively but managed conservatively. (AM J OBSTET GYNECOL 1990;163:1024-32.)

Key words: Ruptured membranes that "reseal," cessation of leakage of amniotic fluid, chorioamnion injury and repair

Preterm prepartal rupture of the membranes continues to be an obstetric enigma in terms of cause and management. This is a frequent problem that complicates 8% to 25% of all pregnancies.[1] Yet there are still major disagreements as to when intervention for delivery should occur and whether antibiotics, steroids, or tocolytic agents should be used.[1-3]

There is one outcome that occurs occasionally, which could have important implications in management. That is preterm prepartal rupture of the membranes with subsequent cessation of leakage of fluid and continuation of the pregnancy. We designate such patients as having had rupture of the membranes that "reseal," although other mechanisms could account for the discontinuation of vaginal amniotic fluid loss and remain to be evaluated. To our knowledge, the characteristics and prognosis of cases that "reseal" have not been described in detail. Information concerning these patients could prove useful in selecting the best management for preterm prepartal rupture of the membranes and might provide insight into the cause. The purpose of this study was to determine in our patient population the frequency of such cases, their epidemiologic features, their obstetric characteristics (including amniotic fluid volumes as assessed by ultrasonographic studies), and their clinical course.

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Material and methods

This case-control study was performed in patients giving birth at Shands Hospital during the years 1984 and 1985. There were 24 study cases with a diagnosis of preterm prepartal rupture of the membranes that subsequently "resealed" with continuation of the pregnancy (study group). Twenty-four women who had preterm prepartal rupture of the membranes but did not "reseal" (control group) were matched to the study group with regard to gestational age at the time of rupture and approximate calendar month of rupture. Data were abstracted from the medical records and included: (1) demographic factors, vital statistics, and socioeconomic indicators; (2) details of past obstetric performance; and (3) characteristics and outcomes of the current pregnancy. All 24 of the study cases and the 24 control cases were singleton pregnancies. Therefore data concerning multiple gestations were excluded from these analyses.

The duration of pregnancy was assigned on the basis of the best estimate derived from menstrual data, early maternal physical examination, early ultrasonographic findings, and the infant's physical and neurologic development. The diagnosis of preterm prepartal rupture of the membranes was based on the history of sudden onset and continued vaginal leakage of fluid, which was confirmed by examination and positive ferning or alkaline testing with Nitrazine paper.[3] Patients with a diagnosis of prepartal rupture of the membranes were routinely hospitalized. In these patients the diagnosis of "resealing" was determined by daily inquiry of cessation of vaginal loss of fluid and by findings on speculum examination of absence of leakage and negative ferning or Nitrazine testing. Patients

with a diagnosis of "resealed" were discharged to outpatient care.

Ultrasonographic studies were performed routinely on most patients with suspected preterm prepartal rupture of the membranes at the time of admission with an ADR model 4000 scanner (Advanced Technology Laboratories, Inc., Bothell, Wash.) that used standard 3.5 or 5 MHz linear transducers. Amniotic fluid volumes were quantitated according to a previously described method.[4] An obvious but slight decrease was designated as "one arrow down." If there was fluid behind the fetal back, but the largest vertical pocket measured 3 to 5 cm, the interpretation was a moderate decrease in amniotic fluid volume, designated as "two arrows down." If there was no fluid behind the fetal back and the largest vertical pocket measured only 1 to 3 cm, the interpretation was a marked decrease, designated as "three arrows down." The most severe decrease in amniotic fluid (oligohydramnios) was diagnosed if there was no fluid behind the fetal back and the largest vertical pocket was less than 1 cm in depth. This was designated as "four arrows down."

Cervical or vaginal cultures for gonorrhea and group B streptococci were obtained on admission. In the event that either culture proved positive, appropriate antibiotic therapy was instituted. Otherwise, and in the absence of choreoamnionitis, antibiotics were not administered. As a general routine during 1984 and 1985, patients with preterm prepartal rupture of the membranes were not treated with tocolytic agents or steroids.

Group comparisons were made with regard to maternal age, past obstetric peformance, race, level of maternal education, marital status, and history of substance abuse. Comparisons were also made between the two groups with regard to: (1) admission characteristics including maternal habitus expressed as weight-to-height ratio, hematocrit, white blood cell count, and ultrasound estimates of amniotic fluid volumes and (2) outcome variables including length of gestation at delivery, fetal birth weight, fetal sex, Apgar scores, perinatal outcome including mortality and neonatal morbidity, and duration of maternal and neonatal hospital stays.

All statistical analyses were carried out by means of the Statistical Analysis Systems,[5] a computer software system for data analysis. For the continuous variables of interest a t test was performed to detect significant differences between the case and control group means. For nominal variables a χ^2 test was performed to test the independence of the outcome variable ("reseal") with the variables of interest. The Wilcoxon rank-sum test was performed for the ordinal response variables. Kendall's tau b test was used for significant linear associations. Since several tests were performed and the sample size was small, the Bonferroni inequality method was used to compute the appropriate level of significance ($p = 0.002$).[6]

Table I. Gestational age at onset of rupture

Gestational age at membrane rupture (wk)	*Preterm prepartal rupture of membrane, 1984-1985*		*p Value*
	"Reseal" (n = 24)	*Other (n = 184)*	
<28	5 (21%)	29 (16%)	0.7
≥28-32	6 (25%)	55 (30%)	0.7
≥32-<36	13 (54%)	100 (54%)	0.99

Results

During the years 1984 and 1985, a total of 24 cases of preterm prepartal rupture of the membranes that "resealed" were identified. This represents 0.4% of all 5937 deliveries, 2.8% of all 843 patients with prepartal rupture of the membranes, and 11% of all 208 patients with preterm prepartal rupture of the membranes.

Among the patients who "resealed," the distribution of gestational age on admission was essentially the same as that observed in all patients in 1984 and 1985 with a diagnosis of preterm prepartal rupture of the membranes that did not "reseal," (Table I). Since the 24 control patients were matched against the 24 "reseal" patients for gestational age at the time of membrane rupture, their gestational ages were identical.

All 48 patients in this pilot project had a history of recent onset of vaginal leakage of clear fluid. All "reseal" patients had either a positive fern test or a positive Nitrazine test. Both tests were performed in 22 of these study patients and both were positive in 17. Patients in the control group tended to initially have greater fluid volume losses by history and 22 had either a positive Nitrazine or a positive fern test result. Both tests were performed in 13 control patients and both were positive in 12. The diagnosis of cessation of amniotic fluid leakage was based on the patient's history and a repeat vaginal examination. No leakage was evident on inspection and all had either a negative fern or a negative Nitrazine test result. Fern tests were performed in 23 of these patients and all results were negative. Nitrazine tests were performed in 12 patients and results indicated acidity in 10. Among these patients the interval between rupture and "reseal" averaged 7.5 days with a range of 2 to 19 days.

Demographic characteristics (maternal age, race, and marital status), socioeconomic factors (level of education), and frequency of substance abuse (tobacco, alcohol, drugs) are presented in Table II for the study and control groups. No statistically significant differences were found between the two groups. However,

Table II. Patient demographics

Variable	Group		p Value
	"Reseal"	No "reseal"	
Age (yr, mean ± SD)	22.00 ± 7.11 (n = 24)	25.54 ± 6.35 (n = 24)	0.07
Race (%)			
Black	25.0	37.5	0.35
White	75.0	62.5	
	(n = 24)	(n = 24)	
Alcohol use (%)			
No	91.7	91.7	0.99
Yes	8.3	8.3	
	(n = 24)	(n = 24)	
Smoker (%)			
No	54.2	68.2	0.33
Yes	45.8	31.8	
	(n = 24)	(n = 22)	
Drug use (%)			
No	87.5	100	0.23
Yes	12.5	0	
	(n = 24)	(n = 24)	
Education (%)			
≤ 12 yr	87.0	92.3	0.29
> 12 yr	13.0	7.7	
	(n = 23)	(n = 13)	
Married (%)			
No	33.0	36.0	0.99
Yes	66.7	64.0	
	(n = 21)	(n = 22)	

Table III. Past pregnancy performance and findings on admission

Variable	Group		p Value
	"Reseal"	No "reseal"	
Prior pregnancies (%)			
≥1 Term (37 wk)	50.0 (n = 24)	62.5 (n = 24)	0.92
≥1 Premature (20-37)	16.7 (n = 24)	25.0 (n = 24)	0.36
≥ 3 Aborted (<20 wk)	0.0 (n = 24)	8.3 (n = 24)	0.05
Height (in) (mean ± SD)	63.7 ± 2.86 (n = 24)	62.5 ± 3.92 (n = 23)	0.23
Weight (lb) (mean ± SD)	144.6 ± 25.47 (n = 24)	150.1 ± 30.78 (n = 20)	0.51
Weight (lb)/height (in) (mean ± SD)	2.27 ± 0.39 (n = 24)	2.42 ± 0.53 (n = 20)	0.29
White blood cell count (No./mm³) (×10³) (mean ± SD)	9.0 ± 2.25 (n = 20)	11.2 ± 3.56 (n = 22)	0.02
Hematocrit (%) (mean ± SD)	32.9 ± 3.53 (n = 22)	34.4 ± 4.16 (n = 24)	0.19

it is important to note that the groups were small and may not have been equivalent.

Table III shows the comparisons of prior obstetric outcomes, as well as the following admission characteristics at the time of initial diagnosis of preterm prepartal rupture: maternal habitus (expressed as weight-to-height ratio), white blood cell count, and hematocrit. Among the control group, 8.3% had a history of three or more previous miscarriages, which was more frequent than the 0% incidence of the study group. The mean white blood cell count on admission tended to be higher for the control group than the "reseal" group. Neither of these trends was statistically significant at a p value of 0.002.

Amniotic fluid volume estimates were performed on admission for all of the patients who "resealed" and 13 of the patients who did not "reseal." The percentages of patients with each of the various quantifications are shown in Fig. 1. Severe reductions in amniotic fluid volumes (↓ ↓ ↓ ↓) were more common in the assessed control patients than in the study patients (69% compared to 4%; $p < 0.0004$). Within the group that "resealed," no significant correlations were found between amniotic fluid volume estimates and (1) the interval from premature rupture of membranes until delivery ($r = 0.29$; $p = 0.15$), (2) birth weight ($r = 0.31$; $p = 0.15$), or (3) gestational age at delivery ($r = 0.26$; $p = 0.22$).

Among the group that "resealed," three were found to have positive vaginal cultures for group B streptococci and all were treated with ampicillin. None of the study patients received tocolytic agents. Among the control population tested, there were no positive cultures for group B streptococci or gonorrhea at the time of admission. Two of the control patients received intravenous β-sympathomimetics. One received intravenous terbutaline to no avail. A second received intravenous ritodrine during transfer, but this was discontinued on arrival at Shands Hospital.

Table IV lists the outcomes in both groups for mean length of gestation at delivery, birth weight, 1-minute and 5-minute Apgar scores, neonatal mortality and morbidity (expressed as frequency of respiratory distress and hyperbilirubinemia), duration of neonatal hospitalization, and duration of maternal hospitalization. The mean length of gestation at delivery in the "reseal" group was significantly longer than that in the control group (Table IV and Fig. 2). Five inductions were performed in the study group. Three were for preeclampsia, one was for a postterm pregnancy, and the fifth was for spontaneous rupture of the membranes at term with prolonged latency. There were five cesarean sections (21%). Two were performed because of arrested active phase of labor, two for fetal distress, and one because of breech presentation. There were no inductions performed in the control group, although four cesarean sections (17%) were performed. The indications were fetal distress (two patients) and breech presentation (two patients).

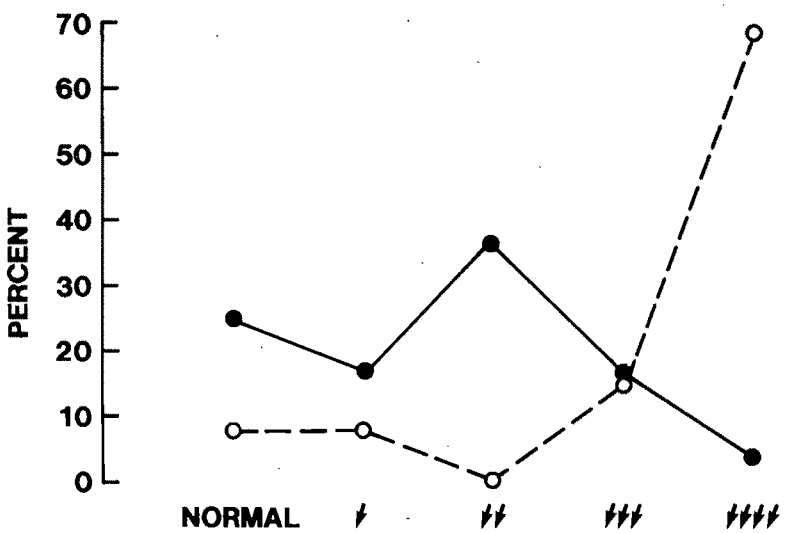


Fig. 1. Graph showing amniotic fluid volume estimates by percentage distributions in "reseal" group *(closed circles)* and control group *(open circles). One arrow down,* Slight decrease; *two arrows down,* moderate decrease; *three arrows down,* marked decrease; *four arrows down,* severe decrease (see text for ultrasonographic method for quantifying fluid volumes). Control group had significantly higher proportion of patients with severely decreased amniotic fluid volumes than "reseal" group ($p < 0.0004$).

Table IV. Obstetric outcome

Variable	*Group*		*p Value*
	"Reseal"	*No "reseal"*	
Gestational age at premature rupture of membranes (wk) (mean ± SD)	29.9 ± 5.3 (n = 24)	29.9 ± 4.9 (n = 24)	
Gestational age at delivery (wk) (mean ± SD)	38.3 ± 2.7 (n = 24)	30.5 ± 4.8 (n = 24)	0.0001
Birth weight (gm) (mean ± SD)	2977 ± 789 (n = 24)	1682 ± 703 (n = 24)	0.0001
1 min APGAR score (mean ± SD)	7.8 ± 1.8 (n = 24)	5.9 ± 3.1 (n = 24)	0.01
5 min APGAR score (mean ± SD)	8.5 ± 1.5 (n = 24)	6.9 ± 3.0 (n = 24)	0.02
Neonatal hospital stay (days) (mean ± SE)	3.3 ± 0.7 (n = 24)	16.4 ± 3.4 (n = 23)	0.01
Respiratory distress (No.)	3 (12.5%)	11 (45.8%)	0.01
Hyperbilirubinemia (No.)	4 (16.7%)	14 (58.3%)	0.003
Fetal neonatal death (No.)	0 (0.0%)	4 (16.7%)	0.11
Maternal hospital stay (days)	10.5 (n = 24)	4.1 (n = 24)	0.025

The distribution of gestational ages at the time of delivery are listed in Table V for both groups. Thirty percent of the "reseal" patients gave birth prematurely (<37 weeks), whereas 100% of the control patients gave birth prematurely ($\chi^2 = 13.6$ with Yate's correction; $p < 0.001$). The mean birth weight of the "reseal" group was significantly greater than that of the control group (Table IV and Fig. 3). Among the "reseal" patients, three infants had body weights below the tenth percentile corrected for gestational age and three infants had birth weights above the ninetieth percentile corrected for gestational age, probably reflecting a normal distribution for these near-term deliveries. All of the infants in the control group had birth weights appropriate for gestational age.

The study group had no perinatal deaths, whereas the control group had four perinatal deaths (perinatal mortality rate = 167/1000) (Table IV). But the difference in absolute numbers of perinatal deaths was not statistically significant ($\chi^2 = 2.8$, Yates' correction; $p < 0.2$). The trend to lower mean Apgar scores at 1 minute and 5 minutes in the neonates in the control group may be attributed to the higher frequency of prematurity. Unfortunately umbilical blood acid-base studies

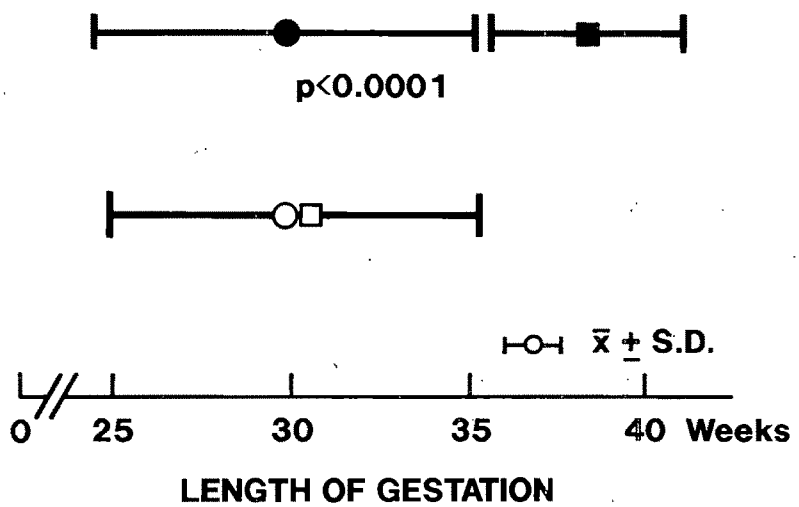


Fig. 2. Graph showing mean (±SD) lengths of gestation at rupture of membranes *(circles)* and at time of delivery *(squares)*. *Solid symbols* represent "reseal" patients; *open symbols* represent control patients. Difference between gestational ages of two groups at delivery was significant ($p < 0.0001$).

Table V. Gestational ages at delivery

Gestational age (wk)	*Preterm prepartal rupture of membranes, 1984-1985*				*p Value*
	"Reseal" (n = 24)		*Control (n = 24)*		
	No.	*%*	*No.*	*%*	
<28	0	0	5	21	0
≥28-<32	1	4	6	24	0.1
≥32-<36	2	8	13	54	0.01
≥36	21	88	0	0	0.001

were not done in sufficient numbers to permit comparisons.

Fifty-eight percent of the infants in the study group were male, as were 54% of the infants in the control group. Neonatal respiratory distress and hyperbilirubinemia tended to occur more often in the control group (Table IV). These and other prematurity problems could account for the trend to longer neonatal hospitalization in the control population (Table IV and Fig. 4). The total duration of hospitalization for the mothers in the study group averaged 10.5 days per patient (range of 3 to 51 days) and tended to be longer than that for the mothers in the control group, which averaged 4.1 days per patient (range of 1 to 9 days) ($p = 0.025$). Two mothers in the control group who gave birth vaginally had a diagnosis of postpartum endometritis and both responded to antibiotic therapy. Within the "reseal" group, four mothers had postpartum endometritis (two vaginal deliveries and two cesarean sections) that responded to antibiotics satisfactorily.

One control patient gave birth with a 20% abruptio placentae at 32 weeks' gestation (after a latent period of 2 days). Another had postpartum hemorrhage severe enough to require blood transfusion. Aside from the duration of maternal hospitalization, maternal morbidity was not thought to be clinically different between the two populations.

Comment

To our knowledge "resealing" in the case of spontaneous rupture of the membranes has not been previously reported in detail. In the 1% to 2% of genetic amniocenteses that may be complicated by vaginal leakage of amniotic fluid, subsequent cessation of leakage and successful completion of the pregnancy has been reported.[7, 8] Gold et al.[9] reported their experience in which six of seven patients (86%) with fluid leakage after second-trimester amniocentesis subsequently ceased leaking and gave birth at term uneventfully. They cited an abstract from the University of Utah Medical Center in which 18 of 22 patients (86%) with amniotic fluid leakage after second-trimester amniocentesis subsequently had "normal outcomes" (Baty B, Weinblatt B. Amniotic fluid leak after second trimester amniocentesis. Proceedings of the NSCG Educational Conference, New Orleans, La., 1988). Yet such outcomes are not commonly acknowledged to occur in the case of spontaneous rupture of the membranes. This raises the question of whether the present large series of cases may represent overdiagnoses.

Garite[10] has stated that history alone gives a correct diagnosis of prepartal rupture of the membranes in 90% of patients. The remaining 10% could have urinary incontinence or vaginitis. It seems unlikely that in

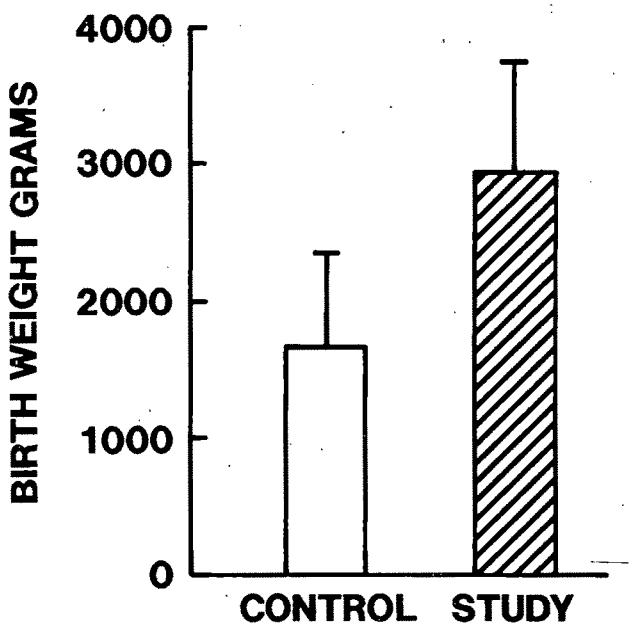


Fig. 3. Mean (±SD) birth weight of "reseal" patients *(cross-hatched column)* was significantly higher than that of control patients *(open column)* ($p < 0.0001$).

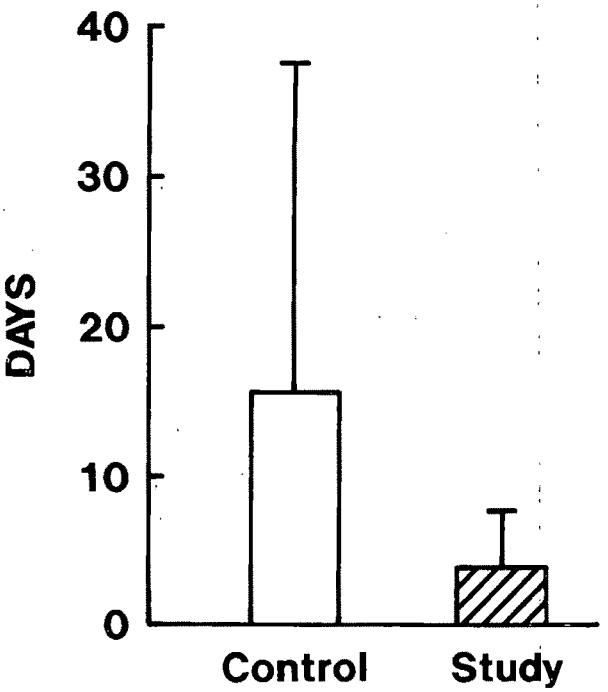


Fig. 4. Mean (±SD) duration of neonatal hospitalization was less in "resealed" group *(cross-hatched column)* than in control group *(open column)*.

the present series patients would initially have either urinary incontinence or vaginitis of sudden onset, would have positive fern or Nitrazine tests, and would then subsequently cease "leaking" without specific treatment. Also the gestational age distribution at diagnosis of rupture for the "reseal" group was very similar to that observed for the total 1984 and 1985 Shands' population that did not "reseal" (Table I). In addition, the demographic and admission features of the "reseal" group appeared to be very similar to those of the matched control population (Tables II and III).

The normal amniotic fluid volumes reported in 25% of our study group do not preclude the diagnosis of spontaneous prepartal rupture of the membranes, since our own experience (Fig. 1) and that of others[11] indicate that spontaneous prepartal rupture of the membranes may be present with normal fluid volumes as assessed by ultrasonographic examination. The 58% frequency of moderate-to-severe decreases in amniotic fluid volumes, (↓ ↓, ↓ ↓ ↓, and ↓ ↓ ↓ ↓) noted on ultrasound in the study group was significantly higher ($\chi^2 = 93$; $p = 0.0001$) than the 5.6% observed in a Shands Hospital population without ruptured membranes.[4] These findings argue against overdiagnosis and support our assertion that these 24 study patients had ruptured membranes. It is possible that the 11% frequency of "resealing" noted in this report is unique to this patient population, but Amon et al.[12] recently reported that the "leaking stopped" in 12% to 13% of their patients with preterm prepartal rupture of the membranes. Additional populations should be studied to establish the frequency of this event.

The outcome data indicate that "resealing" is a desired event. Certainly the results in the neonates were improved. The 12.5% frequencies of fetal growth retardation and macrosomia in the "reseal" group are not much different from the tenth percentile distribution expected in the normal population. Still these frequencies tend to be greater than those observed in the control group. Further studies might establish whether these differences are clinically significant. Commonly feared complications of spontaneous rupture of the membranes, such as chorioamnionitis, abruptio placentae, and septic shock, did not appear to occur with increased frequency in the "reseal" group. Furthermore, the net cost of care would seem to be less in the patients who "resealed." Assuming $1000 per day for neonatal intensive care and $500 per day for maternal care, the net costs for a "reseal" patient would average about $10,300 less per mother and neonate.

Since the rupture-to-reseal interval averaged 7.5 days, it is possible that a more appropriate control group would be one that did not labor for at least 1 week after rupture. Were it possible to adjust for this variable, the magnitude of outcome differences might have been reduced. However, we suspect the "reseal" neonates would still have better outcomes, since the "reseal-to-delivery" interval averaged 7 weeks.

We looked carefully for clinical factors that might influence the advent of "resealing." Of the many epidemiologic and obstetric factors we examined, only amniotic fluid volumes after rupture seemed to be different. We were unable to detect any evidence that infection might prevent "resealing," but we may not have tested for the appropriate indicators.

It seems likely that the smaller the membrane defect resulting in leakage of fluid, the greater the chance of "resealing." The high frequency of "resealing" in genetic amniocentesis favors this hypothesis.[7-9] Even the frequency of overt leakage reported in genetic amniocentesis seems to vary directly with the size of the needle used.[7, 8] In the current study group, the higher prevalence of normal or slightly reduced amniotic fluid volumes suggests that a small aperture promotes "resealing." However, we were unable to demonstrate significant correlations between estimated fluid volumes on admission and the interval until delivery or the gestational age at delivery, in the "reseal" group.

Whether there are therapeutic measures that would enhance or deter the probability of "resealing" remains to be determined. Limited activity and bed rest may favor the reparative process, but to our knowledge no studies have addressed this issue. Also the effect that steroid therapy given to accelerate fetal lung maturity might have on the membrane "resealing" process is unknown.

In summary, a series of patients with the diagnosis of preterm prepartal rupture of the membranes subsequently ceased to leak fluid, continued to carry their pregnancies, and had improved obstetric and neonatal outcomes. In this case-control study we found no clinical factors associated with "reseal" except larger post-rupture amniotic fluid volumes. The frequency of "resealing" must vary among obstetric populations. However, it would appear to be important to search diligently for such cases, since expectant therapy yields excellent results.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. JAMES F. CARTER, Georgetown, South Carolina (Official Guest). Preterm prepartal rupture of the membranes continues to provoke great controversy in obstetrics and gynecology, perhaps because of our inability to both satisfactorily predict and to unfortunately successfully treat this obstetric nightmare in many instances. There are few diagnoses in obstetrics that elicit more concern and anxiety in the clinician.

We have all experienced the anecdotal events of our patients' membranes appearing to reseal. I am not aware of any report that has previously tried to quantitate these events with subsequent prognosis and identification of risk factors.

Dr. Johnson's methodology to match 24 women who had preterm prepartal rupture of the membranes that subsequently resealed (study group) with 24 women with preterm prepartal rupture of the membranes (control group) that did not reseal to the gestational age at the time of rupture and the approximate date of delivery was certainly well thought out. Data abstracted from the records, including demographic factors, vital statistics, socioeconomic indicators, and details of past obstetric performance, gave valuable information in comparison. To simplify the comparison, all pregnancies were singleton.

One of the keys to the study would of course be the accurate diagnosis of rupture of the membranes, and this diagnosis was made quite thoroughly by the means noted, including examination and positive fern-ing and/or results of Nitrazine testing. Because of Dr. Johnson's reference, I assumed that the examination of course would be by sterile speculum. This technique of course is paramount to the examination at the time. The combination of this thorough examination would

be paramount to refuting any skeptic that the rupture of the membranes was the result of vaginitis, urinary incontinence, or both, as Dr. Johnson's study pointed out. I believe this was addressed clearly and concisely.

In an effort to rule out infections as a possible cause and to treat only if positive, cultures were obtained for gonorrhea and group B streptococci, and antibiotic therapy was begun only if positive. It would have been interesting to combine this fact with additional information on the outcome of treatment with tocolytic agents or steroids. What comes to mind would be whether steroids in fact prevented or delayed or decreased the actual percentage of the resealing. It would be interesting to see if the steroids actually decreased the percentage of resealing in patients receiving them. This issue, as pointed out by Dr. Johnson, was not addressed and was not the subject of this article.

Further comparisons were made in regard to maternal age, past obstetric performance, race, level of education, marital status, and substance abuse history. This information was quite thorough. In addition, information that is oftentimes anecdotally reflected on but never, to my knowledge, quite quantitated includes data such as the height versus weight ratio. Hematocrit, white blood cell count, ultrasonographic estimates of amniotic fluid, gestational age at delivery, fetal birth weight and sex, and Apgar scores in perinatal outcome including the mortality and neonatal morbidity were also included. It would have also been interesting to compare the caloric intake of these two groups, which may parallel a positive or negative nitrogen balance. Although this information would be difficult to quantitate objectively, determination of albumin and total protein levels on a multiple serum analysis may be helpful and would certainly be interesting. In general, Dr. Johnson's method was well thought through and gave a valuable objective comparison and may have confirmed or rejected many of our preconceived ideas about the demographics of these two groups.

More and more clinicians are becoming increasingly aware of the importance of amniotic fluid volumes, both in the diagnosis of preterm prepartal rupture of the membranes and in the prognosis. This aspect has recently been discussed in the literature to various degrees of specificity. In this report the numbers have been quantitated, which should help keep this potential resealing event, although the incidence is low, in the forefront of every clinician's mind. Dr. Johnson's group has also made the point that although conservative management may in fact prolong the maternal hospital stay, the decrease in the neonatal hospital stay more than makes up for this conservative approach.

The conservative management is sound obstetric practice, and from a cost-benefit standpoint this report gives the clinician further clout in the ongoing battle with third-party payers who constantly pressure physicians to discharge these patients.

Dr. Johnson's study looked at many risk factors in an effort to identify any fact that may help locate any of these patients that may have a tendency to reseal and therefore improve the neonatal outcome. Many obstetricians are reluctant to engage in conservative management, perhaps partly because they are near level III centers or perhaps because of their fear of increasing maternal morbidity or mortality. Dr. Johnson's article was reassuring in that there was not thought to be any clinically significant difference in mortality and morbidity between the two groups.

One would assume that resealing is a desired event. Dr. Johnson's study would appear to support this assumption; clearly the data show that the larger the amniotic fluid volume, the greater the chance for resealing to occur. Other epidemiologic data did not appear to offer any other suggestions for predicting the resealing, which although somewhat discouraging should not prevent us from continuing to seek out other possible causes as predictors of resealing of the membranes, because it does have such excellent neonatal outcomes in comparison to the patients who fail to reseal.

Continuing this search may enable us to identify therapeutic measures that may be helpful in achieving a better outcome that this study was not able to identify.

One would hope that Dr. Johnson's paper would encourage all of us to seriously consider conservative management of preterm prepartal rupture of membranes, especially in those patients with larger volumes of amniotic fluid. It may also encourage obstetricians who are not ultrasonographers to involve our radiologist colleagues early in the clinical course to help them with any clinical decisions regarding the volume of amniotic fluid. This early and aggressive approach to the evaluation of these patients with ruptured membranes would only help to identify these same patients and help to aggressively seek out this patient population, which although small, has such an excellent perinatal outcome. I think that greater awareness of the options offered by these types of approaches to patient management may be a significant addition to our practice.

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DR. FRANK GREISS, Mooresville, North Carolina. When did you do the analysis of the amniotic fluid volume? Did you do it immediately or later?

DR. JOHNSON (Closing). I agree with Dr. Carter that it would be interesting to have a better idea about the nutritional status of these patients, since that characteristic could have some bearing on the tendency to reseal. About the only way to achieve this is to look at body habitus and the weight distribution to the height of the patient, although that is certainly a very inaccurate measure of nutritional status. The fact that anemia did not seem to be more common in either population seems also a crude indication that their nutritional status was comparable. In answer to Dr. Greiss' question, in general the amniotic fluid volume estimates were done shortly after the diagnosis of rupture of the membranes and certainly within 1 to 2 days after admission.

The use of serial CA 125 concentrations to monitor endometriosis in infertile women

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To evaluate the potential use of CA 125 concentrations in monitoring women with endometriosis, serial determinations were correlated with the clinical course of the disease and pregnancy rates. Preoperative CA 125 concentrations were obtained in 134 consecutive infertile women with endometriosis. Seventy-six (57%) women had values ≥16 U/ml and were followed up for 18 months. At the 6-, 12-, and 18-month intervals, pregnancies occurred in 18 of 45 (30%), 14 of 24 (58%), and 5 of 12 (42%) women in the good prognosis group, respectively; pregnancy rates in the poor prognosis group were 1 of 31 (3%), 2 of 33 (6%), and 0 of 26 (0%) women ($p < 0.001$). Changes in the CA 125 values correlated with the surgical findings in 24 of the 26 women (92%) who had a second-look operative procedure. The study supports the use of serial CA 125 concentrations to assist in the management of women with endometriosis. (AM J OBSTET GYNECOL 1990;163:1032-7.)

Key words: CA 125, endometriosis, infertility

Endometriosis frequently persists or recurs after treatment,[1-3] and often cannot be detected or differentiated by pelvic examination from postsurgical changes. Also, occult foci may be missed even at laparoscopy or laparotomy and result in incomplete surgical removal or destruction of the endometriosis.[4] Consequently, endometriosis often presents a difficult diagnostic and therapeutic challenge to the clinician.

Recently, elevations of CA 125, a serum marker for human epithelial ovarian cancer, have been observed in women with endometriosis.[5-7] In addition, the serum concentrations of CA 125 have been observed to correlate with the clinical stage and the clinical course of the disease,[7, 8] and an earlier study has suggested that the changes of CA 125 may have predictive value for pregnancy.[9] Consequently, this prospective study was undertaken to evaluate further the usefulness of serial determinations in monitoring infertile women after the diagnosis and surgical treatment of endometriosis.

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Material and methods

Preoperative CA 125 concentrations were obtained in 134 consecutive infertile women with endometriosis from whom informed consent had been obtained. Seventy-six (57%) women had values ≥16 U/ml (which is considered elevated in our laboratory), and were followed up for 18 months. Twenty-six of 41 women who

had not conceived underwent a second operative procedure between 12 to 18 months (19 conservative and seven hysterectomy). The characteristics of the initial study population and the subgroup with elevated CA 125 concentrations are listed in Table I. Preoperative evaluation of the couples included semen analysis, postcoital testing, hysterosalpingography, and endometrial biopsy specimen. The surgical treatment of endometriosis was performed by the author and individualized to either operative laparoscopy with electrocoagulation and/or carbon dioxide laser, or conservative laparotomy. The severity of the endometriosis was staged according to the revised American Fertility Society classification.[10] In women with endometriomata, danazol (800 mg/day) was administered for 3 months after surgery. Two patients required donor insemination for a significant male factor, and eight received clomiphene citrate to correct either oligoovulation (five women) or luteal inadequacy (three women).

CA 125 was measured in duplicate with an immunoradiometric assay (Centocor, Malvern, Pa.), which has been modified for use in women with endometriosis, and previously described in detail.[11] The CA 125 levels were not used to influence management decisions, and were evaluated at the completion of the study. The women were considered as having a good prognosis if the postoperative CA 125 concentrations decreased by at least 40% to levels <16 U/ml. Women whose CA 125 concentrations failed to meet these criteria initially or whose levels later increased to ≥16 U/ml, suggesting recurrence, were placed in a poor prognostic group. The data were evaluated with a χ^2 analysis with Yates' correction, and Fisher's exact test. Correlation of the changes in CA 125 values with the clinical course were analyzed with the use of the κ test.[12] A p value < 0.05 was considered statistically significant.

Results

In Figs. 1 and 2 are shown the flow charts for the 45 women in the intial good prognostic group and the 31 women in the initial poor prognostic group, respectively. The number of women in each prognostic group and the number of women who achieved pregnancy are indicated at 6-month intervals. The combined pregnancy rates at the 6-, 12-, and 18-month intervals were 19 of 76 (25%), 16 of 57 (28%), and 5 of 38 (13%) women. During the same time intervals, pregnancies occurred in 18 of 45 (30%), 14 of 24 (58%), and 5 of 12 (42%) women in the good prognostic group, and in 1 of 31 (3%), 2 of 23 (6%), and 0 of 26 (0%) women in the poor prognostic group ($p < 0.001$).

The pregnancy rates at 12 months are listed in Table II, according to the stage of endometriosis at the initial procedure.

Overall, the pregnancy rates were significantly higher in the good prognostic group ($p < 0.001$), and this difference achieved statistical significance in both the moderate ($p < 0.001$) and severe ($p < 0.02$) stages of endometriosis.

Table I. Characteristics of study population with endometrium

Patient characteristics	*Initial group (n = 134)*		*Elevated CA 125 (n = 76)*	
	No.	*%*	*No.*	*%*
Age (yr)				
<26	9	7	4	5
26-29	50	37	30	39
30-35	59	44	30	39
>35	16	12	12	16
Infertility				
Primary	95	71	60	79
Secondary	39	29	16	21
Duration of infertility (mo)				
12-23	35	26	20	26
24-59	74	55	41	54
>59	25	19	15	20
Stage of endometriosis*				
Minimal	18	13	5	7
Mild	35	26	14	18
Moderate	55	41	31	41
Severe	26	19	26	34

*Revised American Fertility Society classification.[10]

The surgical findings in 24 of 26 women (92%) who had a second-look procedure correlated with the changes in the CA 125 values ($p < 0.001$). Endometriosis was found in 23 women, and the two women in whom the values did not correlate had mild disease that was not suggested by values of CA 125, which were <16 U/ml.

Comment

This study confirms and extends the observations in 100 infertile women with endometriosis who were followed up for 1 year.[9] In this earlier investigation, women with elevated preoperative CA 125 concentrations had significantly lower pregnancy rates (45%) than those of women with nonelevated levels (63%). The changes in CA 125 levels had no predictive value in women with nonelevated preoperative concentrations. However, the pregnancy rates were significantly lower in women with elevated preoperative levels whose CA 125 concentrations failed to decrease as compared with the pregnancy rates of women whose concentration decreased. For this reason, a group of women with elevated preoperative CA 125 levels were selected to be followed up until pregnancy occurred or up to 18 months after treatment. In this study, the predictive value of the changes in the pre- and postoperative CA 125 concentrations was again observed, but in addition,

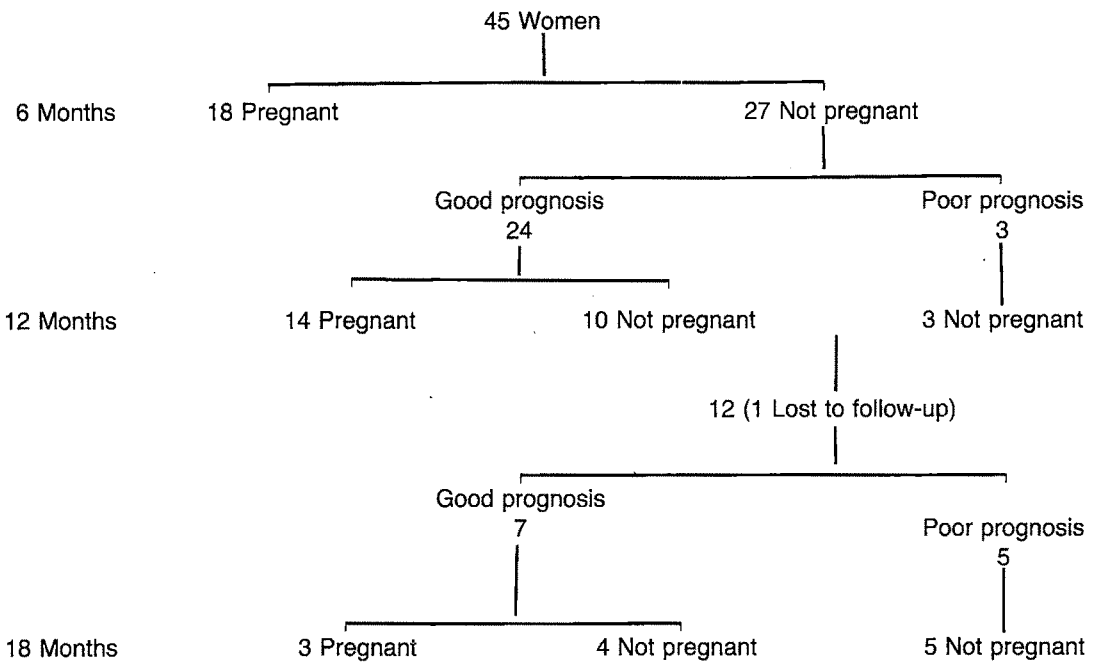


Fig. 1. Flow chart for the initial good prognostic group

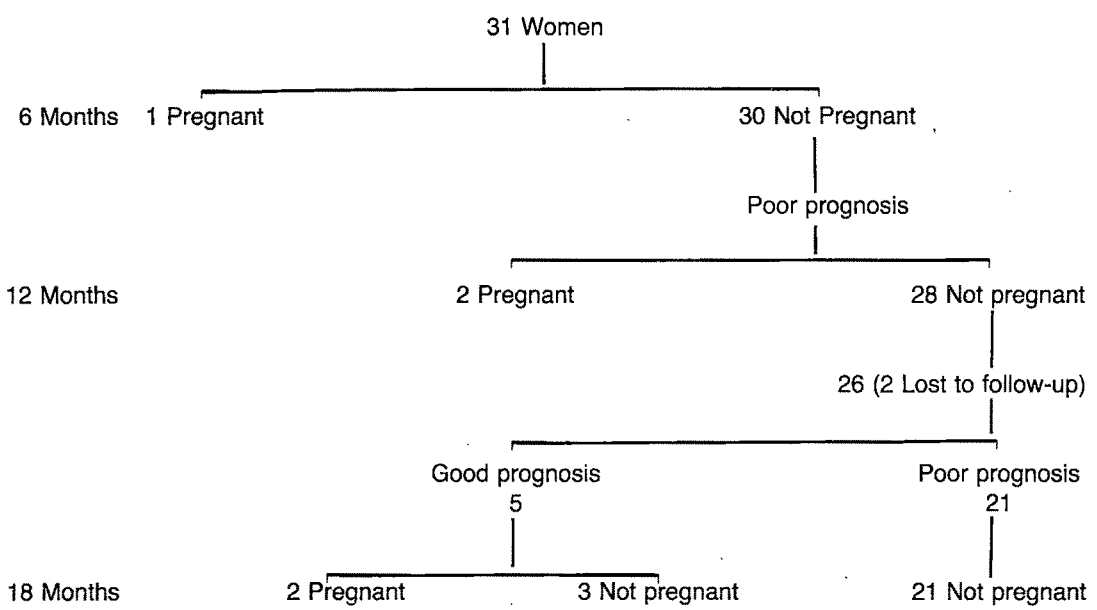


Fig. 2. Flow chart for initial poor prognostic group.

subsequent spontaneous changes such as an increase in levels or changes after retreatment with a reduction in levels also have predictive value for subsequent pregnancy rates.

A high degree of correlation between the surgical findings at a second-look procedure and the changes in CA 125 was found as was seen also in previous observations.[7, 8] However, the degree of correlation is probably inflated because of a number of methodologic biases in the present study. First, only women who had not conceived after 1 year were candidates for a second-look procedure, and second, not all these women were surgically evaluated. Third, women who had obvious recurrence by pelvic examination or symptoms consistent with recurrence would be more likely to undergo another surgical procedure, which is further supported by the high proportion of women who received hysterectomy in this group. Nonetheless, a significant

Table II. Pregnancy at 12 months according to stage of endometriosis

Stage	Good prognosis		Poor prognosis		Total		p Value
	No.	Pregnant (%)	No.	Pregnant (%)	No.	Pregnant (%)	
Minimal	4	2 (50)	1	0 (0)	5	2 (40)	NS
Mild	10	7 (70)	4	1 (25)	14	8 (57)	NS
Moderate	18	15 (83)	13	1 (8)	31	16 (52)	<0.001
Severe	13	8 (62)	13	1 (8)	26	9 (35)	<0.02
TOTAL	45	32 (71)	31	3 (10)	76	35 (46)	<0.001

change in CA 125 concentrations as defined in this study correlated with the status of the endometriosis in most of the women.

Approximately 50% to 60% of women with endometriosis have CA 125 levels ≥16 U/ml in our experience as a surgically oriented university-based referral practice.[7-9] With modification of commercially available assays, serial CA 125 determinations in this group of women appear to offer useful information about the status of endometriosis and the likelihood of achieving a pregnancy after surgical treatment. The changes in CA 125 could be used together with clinical parameters to assist in deciding whether and when surgical or medical retreatment should be considered. Women with a persistently poor prognostic profile of CA 125 values could be counseled to encourage them to think about one of the new technologic approaches such as in vitro fertilization or to begin the adoption process. How much the use of serial CA 125 determinations will assist or improve the overall management of endometriosis will require the results of randomized, prospective studies.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. JOHN A. BURIGO, West Palm Beach, Florida (Official Guest). Dr. Pittaway presented an excellent paper correlating the serum level of CA 125 with the likelihood of achieving pregnancy in patients treated for endometriosis. Most of us associate the clinical use of CA 125 with the diagnosis and management of patients with epithelial ovarian cancers. However, we know that elevations of serum CA 125 can also be associated with some normal physiologic conditions and disease states other than ovarian cancer. Elevations are associated with other malignancies including those of the endometrium, fallopian tube, breast, liver, lung, and pancreas, as well as with benign conditions including endometriosis, pelvic inflammatory disease, pleuritis, pericarditis, and pancreatitis. Elevations are also associated with nonpathologic conditions such as pregnancy and menstruation.

Dr. Pittaway's interest in the correlation between elevations in the serum level of CA 125 and conditions other than ovarian carcinoma precedes this study. In a previous paper he reported the correlation between elevated CA 125 and endometriosis.[1] In that study he reported that the degree of elevation of the antigen correlated significantly with the severity of disease and that changes in the clinical course of patients with endometriosis correlated with changes in the level of circulating antigen. In a more recent study he found that the level of serum CA 125 could be useful in distinguishing between patients with pelvic pain caused by endometriosis versus other causes of pelvic pain.[2] He reported that a CA 125 level ≥16 U/ml correlated with the presence of endometriosis in 80% of the patients and only 6% of patients with elevations had causes for

pelvic pain other than endometriosis. Thus he established a discriminatory value of CA 125 that would be predictive of the presence of endometriosis.

In the current study Dr. Pittaway studied a group of 134 infertile patients. From the initial group he segregated 76 patients who had an elevated level of CA 125, defined as 16 U/ml by his previous publication. His evaluation incuded either laparoscopy with electrocoagulation and/or laser or conservative laparotomy. After surgical evaluation and treatment, each patient had a repeat CA 125 evaluation, and were then classified into either a good or poor prognostic group on the basis of their level. It would be interesting to know how the decision was made regarding operative technique and whether there was a difference in the percentage of patients who converted from the poor to the good prognostic group related to the operative technique that was chosen.

Pregnancy rates were recorded at 6-month intervals for 18 months. The results indicate that the pregnancy rate was significantly higher in the good prognostic group. However, when analyzed by the stage of endometriosis the difference was significant only for those patients with moderate and severe disease. The absence of a significant difference in the patients with minimal and mild disease is disturbing because this group would comprise the majority of patients being seen by the average clinician. I wonder whether Dr. Pittaway would be willing to comment on why the pregnancy rate was not significantly different in lower stages.

He reported that there were 10 patients who received additional therapy for coexisting causes of infertility. He did not tell us whether these patients weighed more heavily on one prognostic group or the other, which could have affected the pregnancy rate within that group.

It would be interesting to know what percentage of the patients with endometriomata who were treated with a 3-month course of danocrine, converted from the poor prognostic group to the good prognostic group.

In his comment Dr. Pittaway suggested that patients with a persistently poor prognostic profile of CA 125 level could be encouraged to pursue adoption or alternative approaches such as in vitro fertilization. With regard to in vitro fertilization, I wonder whether he would be concerned that those patients with persistently elevated antigen are more likely to have residual endometriosis and that immunologic factors in the serum of these patients[3] might lessen the success rate of an in vitro procedure. Perhaps an alternative would be to take those patients who remain in the poor prognostic group after initial surgery and recommend either immediate reoperation for further debulking or medical therapy with gonadotropin-releasing hormone analog, danocrine, or tamoxifen citrate, hoping that they will then convert to the better prognostic group with its associated higher pregnancy rate.

I thank Dr. Pittaway for his excellent presentation and for his earlier work on this topic. The frustration and anxiety experienced by infertile couples increases with the passage of time during their evaluation and treatment. The information presented by Dr. Pittaway enables us to identify a population of patients after the surgical treatment of endometriosis who require additional action. It is hoped that future publications will identify a course of action that will enable us to help these patients to expeditiously achieve their goal.

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DR. BARRY VERKAUF, Tampa, Florida. Dr. Pittaway, have you had the opportunity to follow up CA 125 levels in untreated patients with endometriosis over time and make observations on their stability?

DR. PITTAWAY (Closing). With regard to the surgical technique, this was a clinical study and techniques were really decided on the basis of individualizing with regard to the patient's disease. The majority of the patients underwent laparoscopic treatment. The only relationship to the outcome that was noted was that patients who required conservative laparotomy because of more significant disease were more likely to have persistent or recurrent disease. With regard to the nonstatistically significant difference in the minimal or mild disease, as I mentioned, I would attribute this to the small numbers, and I think if we had had larger numbers the trend that is noted may eventually change the statistical significance. With regard to the information that we provided in the poor prognostic group, I believe that their chances of conceiving over 6, 12, 18 months is very low, and alternatives should be discussed with this group of patients. This would include retreatment, in vitro fertilization, or consideration of adoption. With respect to in vitro fertilization, patients with minimal or mild disease do very well with in vitro fertilization protocols, and in fact are very good candidates with good prognoses. In patients with active disease, particulary with significant ovarian involvement, treatment of the endometriosis is probably worth considering, probably going ahead with in vitro fertilization. The most recent results that have just been published in *Fertility and Sterility* have indicated a delivered pregnancy rate of approximately 12%.[1]

Dr. Verkauf asked about CA 125 levels in patients with untreated endometriosis and patients without endometriosis at all. We have a small number of patients that we followed up over a number of years. In patients without endometriosis the level stays fairly stable. In other words, if the level is approximately 10 U/ml, it will stay approximately 10 U/ml. In patients with endometriosis, particularly those with minimal or mild

disease, we have not had to re-treat them. Again, the levels stay fairly stable unless there is recurrence or progression of disease. We have an ongoing study looking at a number of these patients in which we will correlate second-look data on a separate basis. This appears to show a very good correlation with a rising pattern with the presence or advancement of disease. With most patients who have mild disease we are not pushed to re-treat them as long as the level stays about the same; we continue to monitor them on the basis of clinical information and the CA 125 value.

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Multiple endocrine adenomatosis type I in pregnancy

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A 26-year-old woman, gravida 1, para 0, having episodes of confusion, slurred speech, and blurred vision in pregnancy was documented to have severe hypoglycemia with elevated serum insulin and C-peptide levels. Emergency treatment for hypoglycemia was necessary several times during pregnancy. A healthy female infant was delivered after oxytocin induction of labor. Post partum the patient had numerous episodes of severe hypoglycemia in spite of constant intravenous glucose. Computerized tomographic scan of the pancreas failed to show a lesion, whereas pancreatic arteriography revealed a 2 cm mass in the tail of the pancreas. Partial pancreatectomy was performed 6 days after delivery. Microscopic examination of the tissue confirmed the presence of an insulinoma. Hypercalcemia developed together with elevated parathyroid hormone levels. The presence of an insulinoma, hypercalcemia, and a history of hyperparathyroidism in two relatives indicates that this is a case of multiple endocrine adenomatosis type I first diagnosed during pregnancy. (Am J Obstet Gynecol 1990;163:1037-9.)

Key words: Insulinoma, endocrine adenomatosis

We describe a case of multiple endocrine adenomatosis type I that was first diagnosed during pregnancy.

Case presentation

A 26-year-old, white woman, gravida 1, para 0, was admitted to the hospital at 16 weeks of gestation with symptoms of confusion, slurred speech, and blurred vision. A similar episode had occurred after extreme exercise about 6 months before pregnancy. Otherwise her medical history gave negative findings. Her family history was significant in that her father and paternal grandmother had had parathyroid tumors.

At the time of admission the glucose level was 30 mg/dl. Subsequent fasting values were as low as 18 and 26 mg/dl with elevated serum insulin and C-peptide levels (15 μU/ml and 6.9 ng/ml, respectively). Serum calcium level was mildly elevated at 10.9 mg/dl. Serum cortisol, thyroid-stimulating hormone, and thyroid function tests all were normal. In spite of frequent feedings, repeated hypoglycemic reactions occurred necessitating 24-hour nursing surveillance at home. The hypoglycemic reactions that did not respond to oral feedings were treated with intravenous infusions of 50% glucose and/or glucagon injections.

Periodic ultrasonography of the fetus revealed normal growth and development. Nonstress testing and biophysical profiles were normal. Oxytocin induction of labor was carried out successfully at 41 weeks' gestation. The patient required continuous infusion of 10% glucose throughout labor and delivery to maintain normal serum glucose levels. A normal, 3033 gm female infant, with Apgar scores of 9 and 9, was delivered without complications. Computerized tomographic scanning of the head and abdomen with contrast post partum gave normal results. Pancreatic arteriogram (Fig. 1) with Hypaque revealed a 2 cm mass in the tail of the pancreas. At laparotomy a well-circumscribed mass was present in the distal one third

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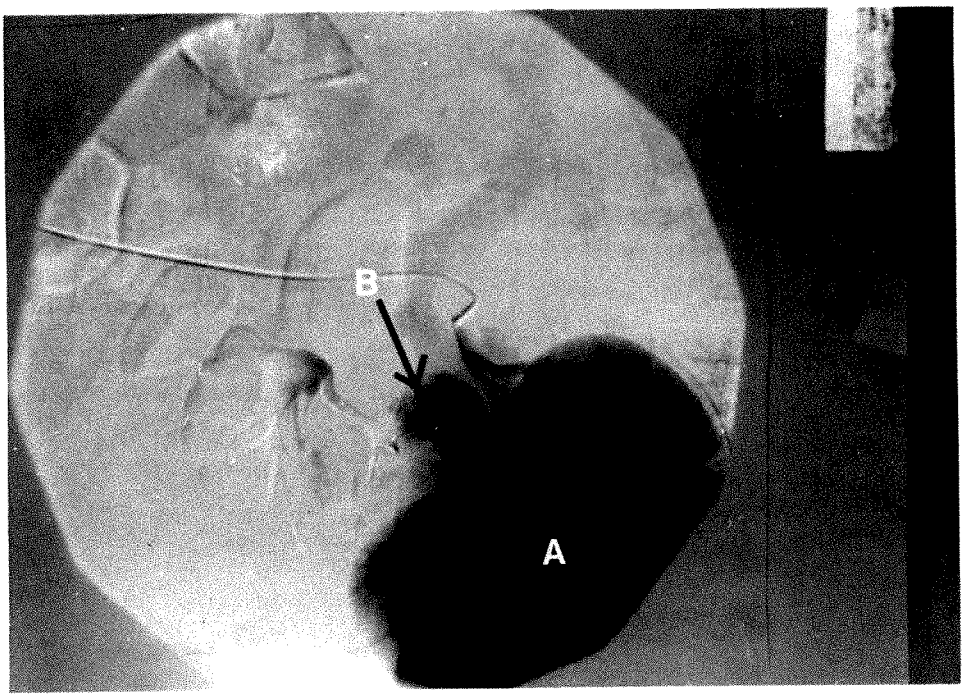


Fig. 1. Arteriogram of splenic artery. *A*, Spleen. *B*, Insulinoma seen in tail of pancreas.

of the pancreas, and because of its location a splenectomy, as well as a partial pancreatectomy, was performed. Microscopic examination revealed large pancreatic islet cells confirming the diagnosis of an insulinoma. The serum calcium level during hospitalization was 10.9 mg/dl. The presence of an insulinoma, hypercalcemia, and a history of hyperparathyroidism in two relatives indicates that this is a case of multiple endocrine adenomatosis type I. There was no evidence of pituitary, bronchial, adrenal, or thyroid adenoma on clinical or laboratory examination.

Comment

The diagnosis of insulinoma is suggested by the clinical presentation of mental confusion, and loss of consciousness with profound hypoglycemia. Other conditions causing hypoglycemia, such as anterior pituitary failure, exogenous insulin administration, use of oral hypoglycemic agents, and renal failure, must be excluded. The diagnosis of an insulinoma will depend on demonstration of hypoglycemia with high insulin and C-peptide levels. Immunoreactive insulin/plasma glucose ratios >0.3 in particular support the diagnosis of an insulinoma.

Insulinoma in pregnancy is extremely rare, and we could identify only 13 reported cases. In these, symptoms began before, during, or immediately after delivery. In approximately half of the cases reported surgical exploration was done during pregnancy; the remainder were treated after delivery. Although invasive diagnostic procedures are relatively contraindicated during pregnancy, the severity of symptoms may dictate surgical intervention during the pregnancy.

Demonstration of the tumor may be difficult with sensitivities of the computerized tomographic scan, arteriography, and preoperative ultrasonography being 35%, 53%, and 59%, respectively. Approximately 10% of insulinomas are not detected by these methods, and surgical exploration may be enhanced by intraoperative ultrasonography, which is said to be 90% effective in localizing the tumor. In this case a mass was demonstrated by arteriography although the computerized tomographic scan failed to reveal the 2 to 2.5 cm. lesion in the tail of the pancreas.

There is some controversy over the effects of hypoglycemia on the fetus as there are reports of spontaneous abortions and embryopathy occurring before 10 weeks of pregnancy and also other reports that suggest that there are no effects on the long-term outcome of the neonate. Undoubtedly, as in this patient, repeated severe hypoglycemic reactions are emotionally stressful and the advisability of intervening surgically before delivery of the infant must be individualized.

Discussion

Dr. Charles R. Whitfield, Glasgow, Scotland. I would like to congratulate Dr. Smythe and his colleagues for presenting this rare case. These insulinomas occur only once in a population of a million so they must be very rare indeed in pregnancy. I also congratulate Dr. Smythe on finding 12 previous reports. In three of the case reports epilepsy was mentioned in

the differential diagnosis. A few patients also are first seen with confusional attacks or even coma caused by hypoglycemia. Only two patients had symptoms for the first time during pregnancy, and two became symptomatic after pregnancy.

Both the diagnosis and the location of these insulinomas are quite difficult. The sensitivities of the various diagnostic techniques are only 35% for computerized tomographic scanning, 53% for arteriography, and 59% for ultrasonography. I wonder why ultrasonography was not used in this case. Our radiologists would expect to detect all insulinomas by ultrasonography, except the rare case in which the pancreas is peppered with tiny microinsulinomas.

I think one of the most interesting things here is the absence of a deleterious effect on the fetus. Looking at the literature, there appears to be absolutely no fetal effect. The one case in which there was an unfortunate outcome of the pregnancy involved a woman who was seen for the first time at about 3 months' gestation with a diagnosis of missed abortion and the first symptoms of hypoglycemia. In all the other 11 pregnancies there was a successful outcome of the pregnancy.

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Dr. E. O. Horger III, Charleston, South Carolina. We should note for all insulinomas, not just those in pregnant women, that >50% of them are found when they are <5 mm in diameter. To find a 5 mm tumor in a pancreas during pregnancy by ultrasonography would, I think, take a whale of a good ultrasonologist.

Dr. Robert Brame, Greensboro, North Carolina. I think it is interesting to consider what causes the symptoms in these cases. Tremor, tachycardia, and sweating in people who become hypoglycemic result from an outpouring of epinephrine. The dizziness, headache, visual disturbances, and mental problems are the products of hypoglycemia and a lack of energy in the brain.

I believe the diagnosis of insulinoma can be made in a case such as this. If the patient is not on a regimen of sulfonylurea and is not using exogenous insulin, there is not much else that will cause severe hypoglycemia with an extremely elevated insulin level. If the patient has hypoglycemia, hyperinsulinemia, and elevated C-peptide levels, that is virtually diagnostic of this disorder. At 16 weeks' gestation perhaps early surgical exploration should have been considered because the diagnosis presumably could have been established.

The diagnostic values of concurrent nonstress testing, amniotic fluid measurement, and Doppler velocimetry in screening a general high-risk population

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To determine the values of individual and combined biophysical fetal surveillance tests in a general high-risk population, we examined 1000 consecutive pregnancies complicated by either postdatism, hypertension, intrauterine growth retardation, or diabetes mellitus. Nonstress tests, amniotic fluid pocket measurements, and umbilical artery Doppler velocimetry were performed on each patient; each test was rated against gestational age–adjusted standards. Clinical end points included perinatal mortality, intrapartum fetal distress, 5-minute Apgar score <7, and neonatal acidosis in pregnancies without major anomalies or extreme prematurity (age at birth >32 weeks), delivered within 72 hours of final tests. Each testing method had specificity >90%. Sensitivities ranged from 69% (nonstress test) to 21% (Doppler velocimetry). Negative predictive values of each method exceeded 85%; positive predictive values ranged from 81% (nonstress test) to 42% (amniotic fluid measurements). The positive predictive value for *any* abnormal test was 54% and increased to 100% when *all* tests were abnormal; this latter condition occurred in only 2% of the total population. Amniotic fluid measurements or Doppler velocimetry, when compared with the nonstress test, appeared to be less powerful "stand-alone" screening tests. The performance of *all* tests in a single session confers little improvement in detection of fetal compromise if the nonstress test is normal; however, this approach may aid decision-making in the management of pregnancies when fetal maturity is not established. (Am J Obstet Gynecol 1990;163:1040-8.)

Key words: Pregnancy, risk screening, nonstress test, Doppler velocimetry, amniotic fluid volume

During the past two decades, a variety of noninvasive fetal assessment tests have evolved to detect possible intrauterine compromise: (1) the nonstress test (NST); (2) multiple parameter biophysical profile testing; (3) semiquantitative assessment of amniotic fluid volume; (4) Doppler velocimetry of umbilical arteries. The NST has become the most commonly used primary test for fetal well-being. It has been associated with high specificity but relatively low sensitivity. Its negative predictive value has been quite high, while its positive predictive value has been much lower.[1] Amniotic fluid volume assessment has been studied in selected conditions such as postdatism and intrauterine growth retardation (IUGR), but previous studies have been conflictual because of their use of different diagnostic criteria.[2, 3] Doppler velocimetry of the fetal umbilical arteries has shown promise in the evaluation of IUGR[4, 5] but its potential for screening unselected high-risk populations is undetermined.[6] While biophysical profile testing may yield better diagnostic performance values, when compared with the NST or amniotic fluid measurements alone,[7, 8] it is labor-intensive and time-consuming; for many clinicians it does not represent a practicable method for screening large populations. Prospective studies that directly compare individual testing methods in general high-risk populations have been limited[9] and have not clearly established the relative values of these approaches. The issue of screening capability is important as the different antepartum tests do not address the same aspects of intrauterine physiologic adaptation and impose different technologic requirements and costs.

We undertook the present study to examine the relative screening capabilities of the NST, amniotic fluid evalution, and Doppler velocimetry in a high-risk population typical of those commonly seen in antepartum testing centers. Using a uniform protocol in which all patients received each test in the same session, we sought to determine the individual and combined abilities of these methods to provide effective screening for intrauterine compromise. In so doing we hoped to establish a better understanding of the actual power of

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Table I. Outcomes of pregnancy and all tests in total group

Indication	Total		Any abnormal outcome		Any tests abnormal		All tests abnormal	
	No.	%	No.	%	No.	%	No.	%
Postdates	428	43.9	78	18.2	94	22.0	2	0.5
IUGR	240	24.6	52	21.7	82	34.2	6	2.5
Hypertension	200	20.5	40	20.0	70	35.0	8	4.0
Diabetes mellitus	106	11.0	18	17.0	26	25.0	0	0
TOTAL	974	100.0	188	19.3	146	15.0	16	1.6

these assessment tools so that improved antepartum management strategies might be developed.

Methods and materials

The study population consisted of 1000 patients, receiving care at the Obstetrics Clinic of the Medical College of Georgia, who were referred to the fetal assessment unit for well-being evaluation. The indications for testing included conditions that are considered to be risk factors for fetal-placental compromise: (1) postdatism, defined as pregnancy entering the forty-second week as corroborated by ultrasonographic dating before 24 weeks; (2) maternal hypertensive disorders, including chronic hypertension and preeclampsia; (3) insulin-requiring maternal diabetes mellitus; (4) IUGR, defined as fetal weight, estimated by sonographic mensuration, to be less than the 10th percentile for gestational age, according to our institutional birth weight standards. The distribution of testing indications is shown in Table I.

Fetal testing was performed between the gestational ages of 28 and 43 weeks, in accordance with an institutional protocol, and is further described for each method. For all tests study conditions were standardized for time of test (8 AM to 2 PM); maternal diet (2 hours postprandial), position (semi-recumbent), and activity (at rest for at least 1 hour); patients were instructed to refrain from smoking. All tests were performed by the same team of observers, using the same technical approaches.

The NST was conducted for a minimum of 30 minutes, with an electronic fetal heart rate (FHR) monitor in the Doppler mode, hard-wired to a microcomputer, driven by a previously described software program for archiving and analysis of baseline FHR.[10] A test result was considered normal if baseline rate, long-term variation, and incidence of accelerations and decelerations met institutional standards, adjusted for gestational age.[11] For the study group this meant that the mean baseline FHR was <155 or >120 beats/min, the coefficient of baseline FHR variation exceeded 0.02, at least three accelerations exceeding 15 beats/min amplitude and 15 seconds' duration were present, and no repetitive variable or late decelerations occurred. A test result was considered abnormal if two or more of these parameters fell >2 SD from the normal population means.

Amniotic fluid pocket evaluation consisted of determining the vertical and horizontal dimensions of the largest pocket visualized by real-time ultrasonography. Pocket measurements were related to gestational age standards[11]; a maximal pocket falling >2 SD below the normal mean was considered to represent reduced amniotic fluid volume. At all gestational ages the minimal dimensions of the largest visualized pocket should have exceeded 2 × 2 cm.

Doppler velocimetry was performed with a continuous wave probe, operating at 4 MHz, on an ultrasonographically localized midportion of umbilical cord. Studies were performed in the absence of fetal breathing and included at least 10 to 15 continuous cardiac cycles for the determination of mean systolic peaks and diastolic troughs to obtain a systolic/diastolic (S/D) ratio. Each velocimetry study consisted of three separate insonations, and these values were averaged to achieve a final S/D ratio. The S/D ratios were then rated against an institutional nomogram for gestational ages between 28 and 42 weeks. An abnormal value was considered to be either an S/D ratio exceeding the 90th percentile for gestational age or the observation of absent or reversed end-diastolic velocities. The cutoff for maximal S/D ratios varied with gestational age and showed a progressive decline from 28 through 42 weeks of gestational age. At 28 weeks the threshold for maximal S/D ratio was 4.15; at 32 weeks, 3.70; at 36 weeks, 3.50; at 42 weeks, 3.10.

Testing sessions were conducted at least weekly for pregnancies between 28 and 32 weeks and at least biweekly thereafter. Clinical management used test results to determine the need for subsequent interventions, according to the scheme shown in Fig. 1.

Obstetric outcomes for each pregnancy were examined for the presence of perinatal mortality, intrapartum fetal distress necessitating cesarean section or operative vaginal delivery, 5-minute Apgar score <7, and neonatal mixed or metabolic acidosis. Five-minute Apgar scores of <7 were considered only for infants when gestational age alone was not a confounding variable,

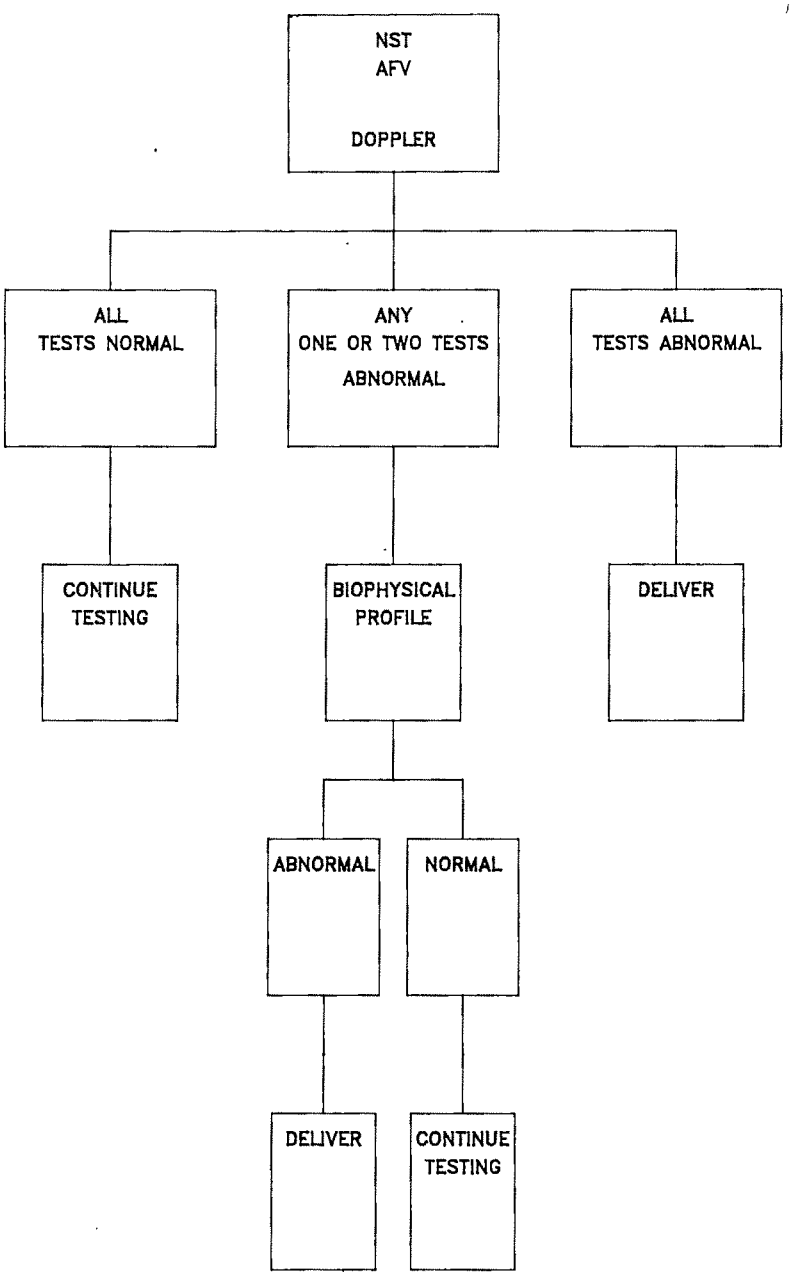


Fig. 1. Management of algorithm of antepartum testing used in study.

i.e., beyond 36 weeks. Neonatal acidosis was considered only when the umbilical arterial pH was <7.20 *and* the base excess exceeded −8.0 mEq/L.

Sensitivity, specificity, and positive and negative predictive values were determined for each test individually and in combination. Test sensitivities were rated against false-positive rates (1 − Specificity) with the use of receiver operating characteristic plots. Comparison between groups was performed by χ^2 tests, with a p value of <0.05 considered as significant.

Results

One thousand patients were evaluated according to the study protocol outlined in Methods and materials for the high-risk conditions listed in Table I; 26 patients were excluded from final statistical analysis because of the presence of significant anomalies detected at birth, multifetal gestations, confirmed gestational age <28 weeks at delivery, delivery outside the institution, or unavailability of umbilical cord blood gas values.

Obstetric outcomes of study group. One hundred

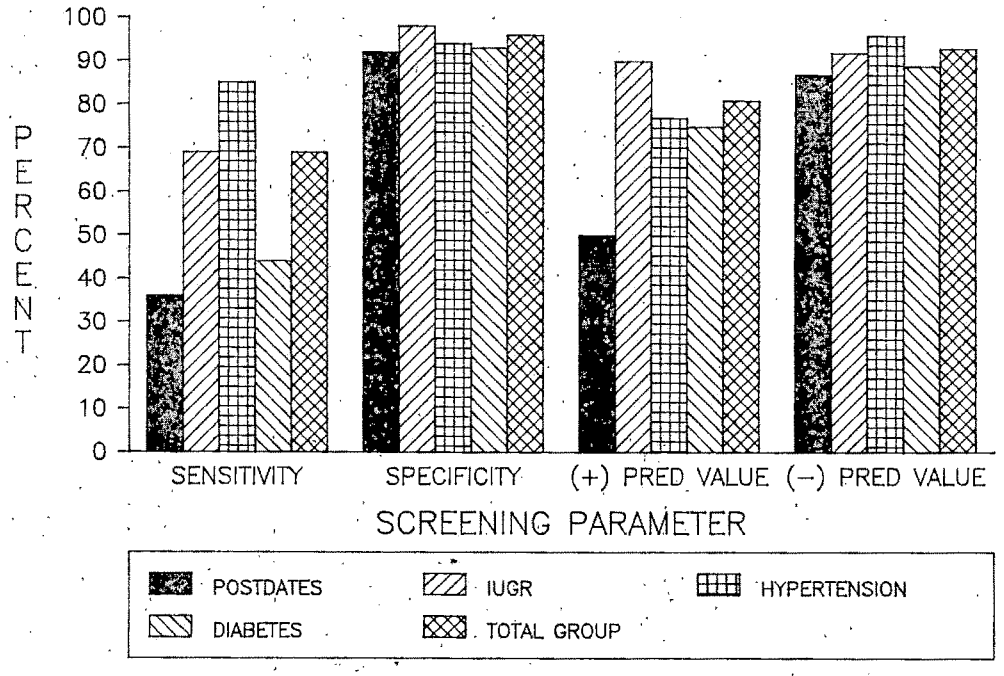


Fig. 2. Distribution of screening parameters associated with NST in study population.

eighty-eight fetuses or 19.3% of the total group had at least one of the previously described perinatal complications: antepartum death ($n = 1$); neonatal death ($n = 1$); intrapartum fetal distress ($n = 164$); 5-minute Apgar scores <7 ($n = 106$); neonatal acidosis ($n = 90$). The distribution of complicated outcomes, according to risk factors, is shown in Table I and was not significantly different among the individual risk groups. There were no perinatal deaths after normal antepartum tests. All patients were delivered of their infants at or beyond 32 weeks' gestational age. Mean (±SD) gestational age at delivery for fetuses in the IUGR, hypertension, and diabetes groups was 38 ± 1.2 weeks; mean (±SD) gestational age at delivery for the postdates group was 41.9 ± 0.3 weeks.

Test performance of study group. Figs. 2 to 4 show the screening performance of the final individual test results, obtained before delivery, for the total study group and the individual risk conditions surveyed. The mean (±SD) number of studies was 4.2 ± 2.2 for each patient in the IUGR, hypertension, and diabetes groups and 2.3 ± 1.2 in the postdates group. The 974 patients analyzed underwent a total of 3277 tests. The NST had the most frequent abnormal results (16.2%), followed by amniotic fluid assessment (10.6%) and Doppler velocimetry (8.2%). For any single test in the total study group the sensitivity was 78%; specificity, 85%, positive predictive value, 54%; and negative predictive value, 85%. Among the single assessment methods the NST had the highest sensitivity for the total study group and its individual risk categories; it also showed the highest positive predictive values for the entire study group (Fig. 2). There were significant differences among the individual risk groups for NST sensitivity, being highest in pregnancies complicated by hypertension (85%) and IUGR (69%). Similar trends were noted among the individual risk groups for NST positive predictive values (Fig. 2). Amniotic fluid assessment had lower sensitivity among all individual risk categories, ranging from 45% (hypertension) to 21% (postdatism); its positive predictive values were below 50% in all groups except for diabetes, in which it was 75% (Fig. 3). Doppler velocimetry had the poorest individual performance among all risk groups with a sensitivity ranging from 0% (postdatism) to 45% (hypertension); its positive predictive value fell below 50% in all risk groups except for hypertension (75%) (Fig. 4). Measures of individual test specificity and negative predictive values exceeded 80% in the total group and were not significantly different among the various risk categories.

Sensitivities, specificities, and predictive values for the test combinations in the total study group and all risk conditions are shown in Table II. The combined occurrences of all test results being abnormal had a positive predictive value of 100% and a false-positive rate of 0% but was observed in only 2% of the total study group. Receiver operating characteristic curves for individual tests and their combinations are shown

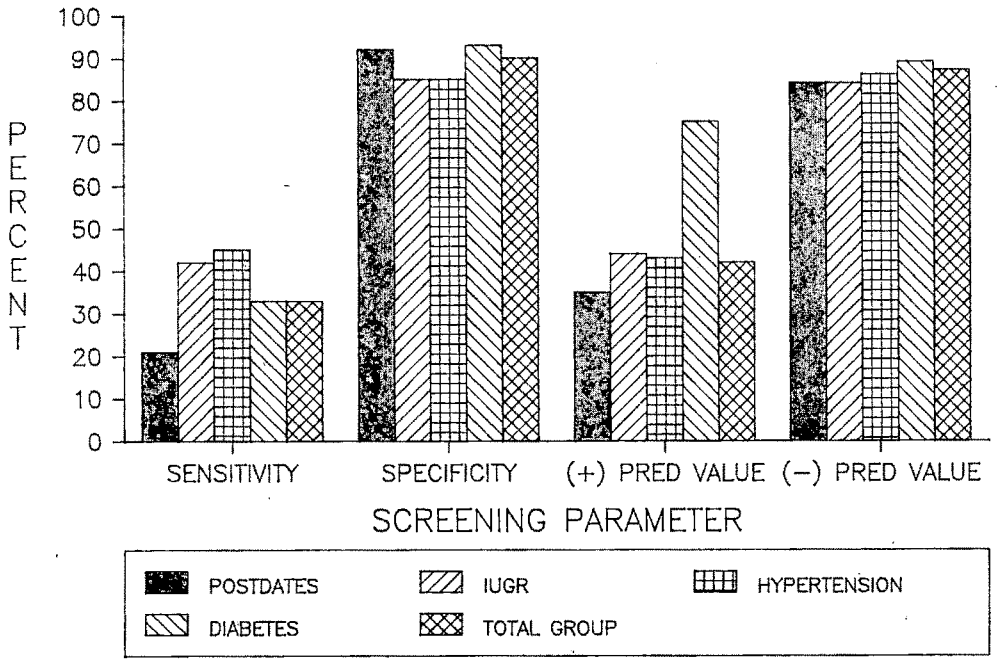


Fig. 3. Distribution of screening parameters associated with amniotic fluid assessment in study population.

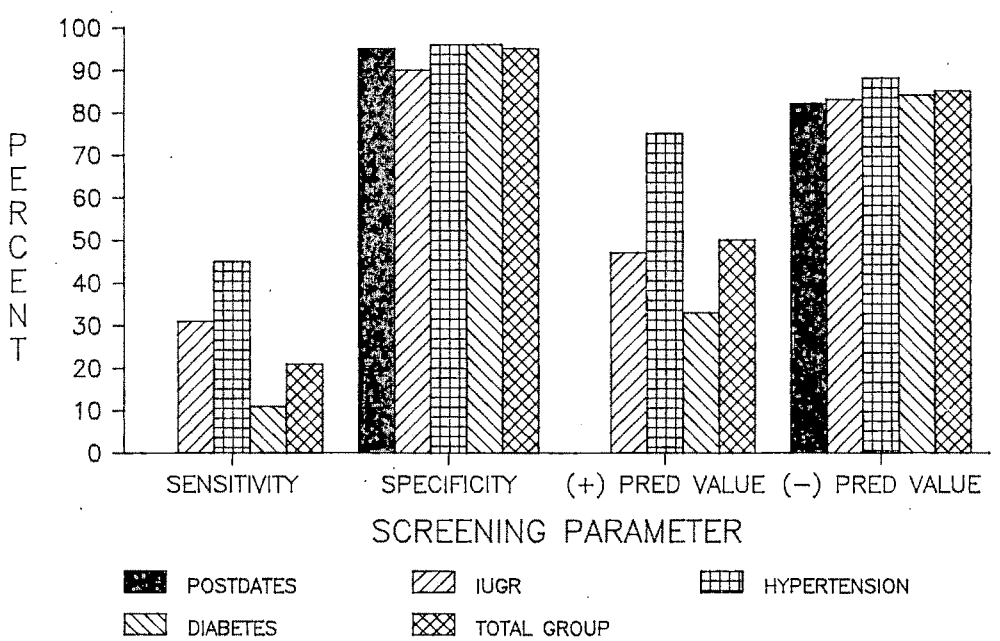


Fig. 4. Distribution of screening parameters associated with Doppler velocimetry in study population.

for the individual risk conditions in Fig. 5. This rating is based on the deviation of the plot from an ideal line passing through a false-positive rate of 0% (X axis) and sensitivity of 100% (Y axis). For the total study group and the individual risk categories the NST alone either equaled or exceeded the other individual tests or their combinations when rated in this fashion.

Comment

This study has examined the relative screening capabilities of antepartum tests that are commonly used to evaluate general and specific categories of fetal risk. Our goals were to determine whether any individual test or test combinations provided better screening performance in such a population and whether certain

Table II. Screening performance of test combinations in study group*

Indication	*Tests*	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*
Postdates	NST + AFV	18	100	100	85
	NST + Doppler	18	99	78	83
	AFV + Doppler	3	100	100	83
IUGR	NST + AFV	38	98	83	85
	NST + Doppler	24	100	100	83
	AFV + Doppler	31	100	100	80
Hypertension	NST + AFV	40	95	67	86
	NST + Doppler	40	100	100	87
	AFV + Doppler	20	100	100	83
Diabetes	NST + AFV	22	100	100	86
	NST + Doppler	0	100	ND	83
	AFV + Doppler	0	100	ND	83
Total group	NST + AFV	29	99	82	85
	NST + Doppler	17	99	89	85
	AFV + Doppler	9	99	73	85

AFV, Amniotic fluid volume; *ND,* not determinable.
*Values expressed as percentages.

modalities might be better suited for some risk conditions than for others. Prospective antepartum management was undertaken with the null hypothesis that each testing method was an equipotent screening tool. As no previous similar studies existed, there was no apparent reason to assume a priori superiority of a single testing approach. To provide further means of comparing test performances, each test was performed on all patients, proximate to their delivery, under a uniform study protocol. Test results were rated according to values derived from normal patients of comparable gestational ages. Finally, common objective pregnancy end points were chosen for evaluating all testing methods.

We found that the individual tests and their combination had similar abilities to detect fetuses who were at low risk for compromise, as judged by test specificity and negative predictive values, regardless of the antecedent risk factor that prompted antepartum evaluation. However, the NST appeared to be the most sensitive single test. Its positive predictive value equaled or exceeded that of amniotic fluid assessment or Doppler velocimetry in all risk conditions. This finding is consistent with what might have been anticipated from earlier studies of multiple parameter biophysical testing[7, 12] but differs from expectations generated by previous investigations that focused on amniotic fluid assessment[13] or Doppler velocimetry.[14, 15] These previous studies were performed on different obstetric populations, used different standards for test rating, and therefore cannot be considered directly comparable to the present investigation. Most past studies have also used arbitrary rating schemes for test assessment; these schemes are usually not related to normal gestational age standards and might not apply equally well to general high-risk populations, studied over a broad range of the third trimester. Further, the influences of test results on subsequent management were undoubtedly different for the other published studies; this may have introduced a bias that could either strengthen or weaken the apparent performance of a specific screening test.

We also found that individual or combined testing methods did not provide similar screening performance when evaluated in the context of individual risk conditions. This is illustrated by the higher sensitivities of the NST or amniotic fluid assessment for IUGR and hypertensive groups than for postdates or diabetic groups and the considerably higher sensitivities of Doppler velocimetry for these same risk conditions when compared with postdates pregnancies. These findings could reflect the different causes of fetal compromise that these risk conditions engender rather than the prevalence of fetal compromise itself, which was similar for all individual risk conditions.

While it might appear that individual methods, notably, the NST, were superior screening tools for our population, it should be recognized that positive predictive errors also were highest when only single testing methods were considered. Approaches that combined the NST with either Doppler velocimetry or amniotic fluid assessment decreased this type of error to nearly 0%. This becomes an important consideration when testing is performed before the establishment of fetal maturity and when only one of the testing methods yields an abnormal result.

The potential cost-effectiveness of screening approaches is difficult to assess since the costs for patient testing may vary widely among institutions. In this particular study the cost of the NST was $75 per test and amniotic fluid evaluation added $25 to this figure. As this investigation began before Food and Drug Administration approval of Doppler velocimetry for clinical

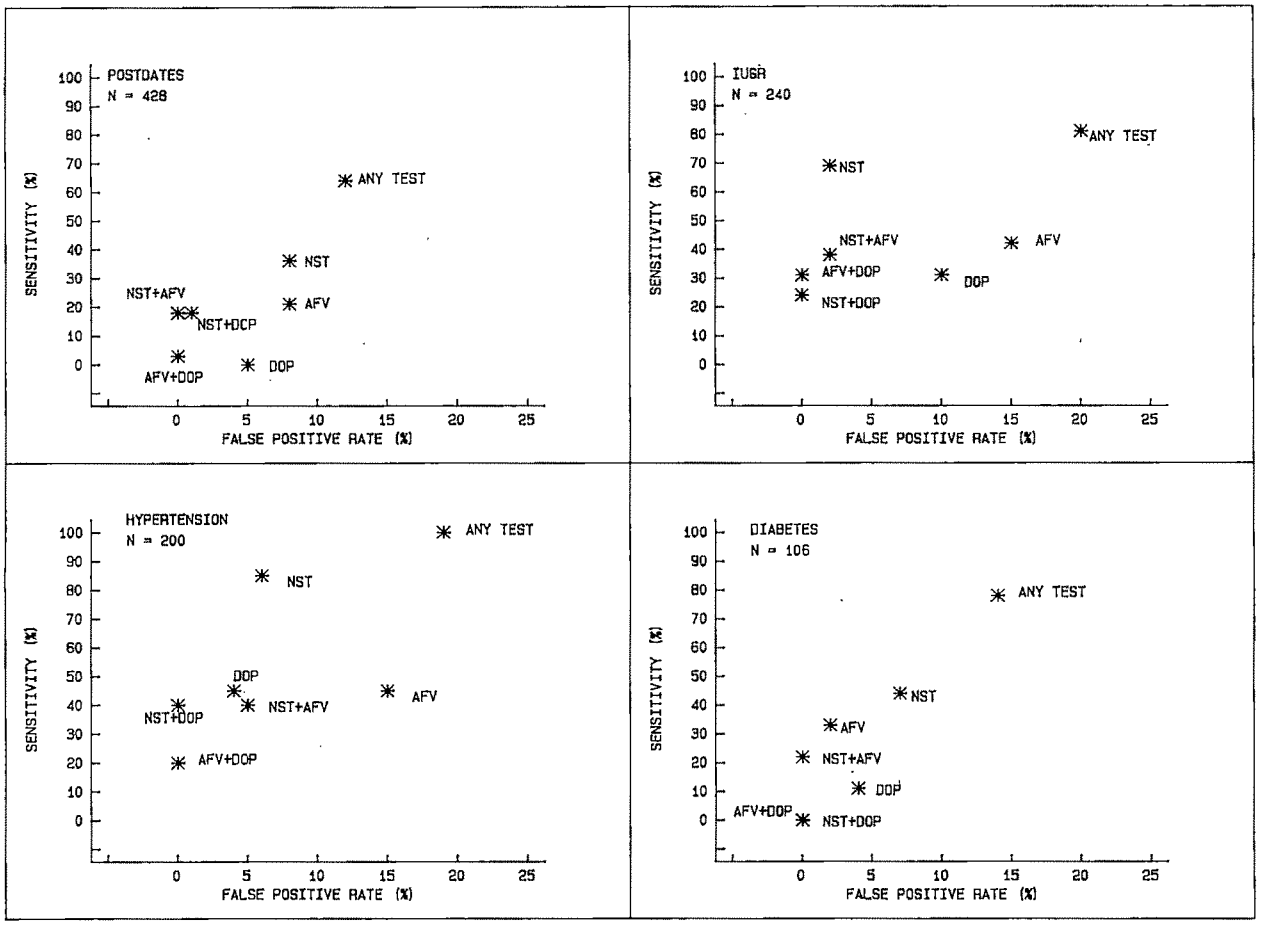


Fig. 5. Receiver operating characteristic plots for all tests in each risk category. Values for each test are labeled in plots according to individual or combined tests. *AFV*, Amniotic fluid assessment; *DOP*, Doppler velocimetry.

application, this latter test was not considered for patient billing; Doppler velocimetry charges are currently an additional $25 per test. On the basis of the 3277 tests performed in the entire group, the cost per patient would have averaged $330, as compared with a mean daily cost of hospitalization for a normal vaginal delivery of more than $500, excluding charges for labor and delivery care. The cost of a single day of neonatal intensive care (which might have been avoided by timely intervention) during the time of the study averaged $1500 in our hospital; the average length of admission to the neonatal intensive care unit for sick infants older than 32 weeks was approximately 14 days, if for reasons other than prematurity. The overall cost of this testing program, approximately $410,000, would be counterbalanced by preventing 20 neonatal intensive care admissions. Finally, the perinatal death rate associated with this approach was 2.1 per 1000 or approximately one third of that noted in our institution for nonanomalous infants delivered at or beyond 32 weeks' gestational age, during this time period.

We may draw the following conclusions from this study. First, in all risk conditions examined, the NST was superior to the other testing methods when viewed as an individual test. As a corollary, neither amniotic fluid assessment or Doppler velocimetry should be considered as an adequate, "stand-alone" antepartum screening method. Second, the screening power of any individual test varies with risk condition. In particular, it would appear that no individual or combined testing method is a very sensitive screening tool for pregnancy complicated by postdatism or diabetes mellitus and that the occurrence of these risk factors might be better served by other testing techniques, such as multiple parameter biophysical testing or contraction stress testing. This issue merits future prospective evaluation. Third, combinations of these screening tools, performed at the same session, may improve the accuracy of prediction of fetal compromise and should be strongly considered when the fetal maturity is not established. Finally, the development of objective, age-related reference standards and the accumulation of

substantial clinical experience with the antepartum evaluation of specific risk entities should be undertaken in all testing centers that assess large numbers of high-risk pregnancies. This would enable better contextual evaluation of the antepartum tests used in screening high-risk pregnancies and could lead to more appropriate bases for clinical decision-making.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Karen L. Ferguson, Palm Bay, Florida (Official Guest). Antepartum identification of the fetus at risk for preventable morbidity or mortality remains the major challenge of modern obstetrics. An optimal test method would assess fetal status and ultimately reduce prenatal morbidity and mortality. The testing process must be cost-effective, accurate, sensitive enough to detect pregnancies at risk, and specific enough to identify pregnancies that will have a good outcome.

Methods for determining fetal risk that are currently in use have a high false-positive rate. False-positive results encourage unnecessary obstetric intervention and increase the risk of maternal and fetal morbidity. Establishing safe parameters for intervention is the hallmark of a meaningful study protocol.

The study presented has several strengths. The study design is prospective. The number of subjects is large enough to allow analysis of the collected data. Additionally, the authors have made an effort to control extraneous variables. The tests were standardized for time of day, postprandial state, maternal position, activity, and avoidance of smoking. Unfortunately, the study used birth weight standards that were based on institutional norms that were not described in the paper. It is impossible to compare the results with previously published studies. In addition, an institutional nomogram was used to determine abnormal ratios of systolic/diastolic pressure. In addition, amniotic fluid pocket evaluations were based on institutionally developed norms that were not described in the article. Since amniotic fluid pocket norms were not given, comparison of the authors' results with those published by other institutions cannot be made.

Although the study design of this article is commonly used, it is fundamentally flawed. The study does not address the central issue of the usefulness of antepartum tests in preventing an adverse neonatal outcome. An adequately designed study would be unethical and would not be feasible. An adequate study would prospectively and randomly assign patients to the three tests used and then allow the pregnancies to follow their natural course without intervention. Clinicians in this study group, however, were advised of test results and subjectively altered the clinical outcome by altering their plan of care. Clinical intervention guided by a false-positive test result could inappropriately alter a patient's clinical course. The authors of this article did not present data describing the frequency of type of intervention, such as induction of labor or cesarean section, when a test result was abnormal.

This study suggests that a poor outcome can result in spite of physician intervention in response to abnormal test results. One would have to question the value of prognostic or screening tests that will not alter fetal risk. Considering the overwhelming ethical and philosophical constraints, the authors should be congratulated on their study design.

Although the authors did not include a physiologic discussion of the superiority of the NST as a screening tool, this article does bring into focus the important issue of the multifactorial etiology of fetal compromise. Since a variety of disease states can complicate pregnancy and cause intrauterine compromise, it is logical

to carefully examine and compare a combination of methods of fetal surveillance, with measurement of different aspects of maternal-fetal physiologic parameters. It is only through carefully executed studies such as this one, which examine physiologic responses in each high-risk disorder, that the clinician is ultimately guided to choose the proper combination of antepartum tests and to evaluate and act on intrauterine compromise.

Dr. Ronald V. Wade, Charlotte, North Carolina. I would like to congratulate Dr. Devoe on a very nice article and applaud him on 1000 cases reviewed. I understand the magnitude of that effort. Two quick questions: Since a lot of the abnormal outcomes were classified as "fetal distress," would you elaborate on what those were? Were they fetal monitoring data or otherwise? Second, do you have a breakdown of the sensitivity, specificity, and predictive values that are based only on the outcome variable of cord pH?

Dr. Salih Yasin, Miami, Florida. I appreciate the rich article with all the information. We are still looking for the ideal test. People who are in monitoring probably would admit that there is no ideal test. The reason for this is that we always expect babies to behave in a mathematical fashion, which is not how they behave. There are still biologic entities that behave differently with different situations. We do not find in the data presented any statement of the influence of the maternal condition on intervention. Ultimately, with all the testing, it is really the maternal-fetal unit that determines part of the outcome.

Dr. Robert Bowden, Lynchburg, Virginia. I would like to know if Dr. Devoe would share with us any data on the 26 patients he excluded because of fetal abnormality.

Dr. Devoe (Closing). Perhaps what I should do first is address the point made in the discussion about standards. Most of our biophysical standards that we used in the study have been previously published and are referenced in the article itself. Second, we have found, in looking at amniotic fluid volume, Doppler velocimetry, and birth weight, that if you take any one of these three parameters to various institutions you find that the populations are not particularly continuous or overlapping. I would recommend that those interested in using such reference points probably ought to develop their own standards and base their discrimination on their own population rather than adopting that developed by somebody else, working with perhaps a significantly different group of patients.

Dr. Wade raised an issue regarding abnormal outcomes of fetal distress. Fetal distress was defined in most cases by a combination of fetal heart rate patterns (changes such as persistent late decelerations, loss of beat-to-beat variability, sustained tachycardia or bradycardia, or severe variable decelerations). All instances were corroborated by scalp pH. As far as breaking these down into cord pH alone for fetal acidosis, I don't have the data but they are available.

Dr. Yasin's points are very well taken. I think the issue here was not so much to define an ideal test but rather to take more of a real-world view and try to sort out the very confusing situation of how one addresses the multiplicity of tests available and to pick what might represent the most reasonable screening methods available. We must recognize that they may all have flaws but all of these methods have been championed to some extent to the exclusion of other methods. What we really tried to do was to put some balance back into an unbalanced situation. I think that was the main thrust of this particular study, and we knew before we started that it was unlikely we were going to find a method that was unerring and perfect. This would have been a remarkable accomplishment for anybody.

The final question dealt with the patients who were excluded. I do have data for these patients in our files, but the reasons that most of them were excluded was that their good or bad outcomes were due to problems that would not necessarily have been pertinent to the testing method or they were delivered outside our facility and data collection was not done in the same way as it was done for all the other patients. The cord blood gas values were unavailable in such circumstances so we could not evaluate our end point of neonatal acidosis. That is the main reason why they were not included.

Eclampsia

VI. Maternal-perinatal outcome in 254 consecutive cases

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During a 12-year period, 254 cases of eclampsia were managed at this center. Eighty patients (32%) did not have edema, 58 (23%) had "relative hypertension," and 49 (19%) did not have proteinuria at the time of convulsions. Eclampsia developed at ≤20 weeks in 6 patients and beyond 48 hours post partum in 40 (16%). Convulsions developed in 33 while they were receiving standard doses of magnesium sulfate for preeclampsia during or after birth, and subsequent seizures developed in 36 (14%) after magnesium sulfate therapy was started. There was one maternal death (0.4%) and morbidity was frequent (acute renal failure, 4.7%; pulmonary edema, 4.3%; cardiorespiratory arrest, 3.1%; and aspiration, 2%. The use of multiple drug therapy was associated with significant maternal and neonatal complications. The total perinatal mortality was 11.8%, with the majority of them related to either abruptio placentae or extreme prematurity. These findings emphasize the need for intensive monitoring of women with preeclampsia throughout hospitalization and underscore the importance of maternal stabilization before and during transfer. (Am J Obstet Gynecol 1990;163:1049-55.)

Key words: Eclampsia, complications, perinatal outcome, maternal transfer

Eclampsia is defined as the onset of convulsions or coma during pregnancy or post partum in a patient who has signs and symptoms of preeclampsia. According to Chesley,[1] a description of this syndrome was mentioned in the ancient writings of both the Egyptians and the Chinese. In recent years the reported incidence of eclampsia ranged from 1 in 110 to 1 in 3448 pregnancies.[2-4] The extremely low incidence reported from Sweden indicates that appropriate prenatal care and early hospitalization of patients with preeclampsia will prevent most cases of eclampsia.[3] Similar findings were reported by Zuspan,[5] as well as by Gilstrap et al.[6] The latter study demonstrated that eclampsia was rarely encountered in patients with proper management who had early and prolonged hospitalization for mild pregnancy-induced hypertension. The study included a total of 545 women who were hospitalized at 25 to 38 weeks' gestation. The duration of hospitalization ranged from 2 to 120 days (average 24 days) with only one patient (0.2%) having eclampsia.

Eclampsia is a life-threatening emergency that continues to be a major cause of serious maternal morbidity and is still the leading cause of maternal mortality worldwide. Complicated cases and mismanaged cases are responsible for most maternal deaths, which are usually due to intracerebral hemorrhage, pulmonary edema, or renal, hepatic, or respiratory failure.[4] In addition, its presence is usually associated with high perinatal mortality and morbidity. The main causes of perinatal mortality and neonatal morbidity from eclampsia are preterm delivery, fetal growth retardation, and abruptio placentae.[4]

At this institution, which is a tertiary referral center for five states, the incidence has remained at about 1 in 320 deliveries for the past 30 years. The factors responsible for this high incidence have been the subject of a recent report from this institution.[7]

During the past 12 years, 254 cases of eclampsia were managed at this perinatal center. The purpose of this study is to evaluate the clinical course and outcome in these patients with emphasis on the pitfalls in the diagnosis and management of eclampsia.

Material and methods

From Aug. 1, 1977, to April 30, 1989, 254 consecutive cases of eclampsia were managed at E. H. Crump Women's Hospital and Perinatal Center, Memphis. The study population and methods used have been described previously.[7-10] Patients with other causes of convulsions were excluded. All patients with atypical onset of eclampsia had a special neurologic evaluation to rule out the presence of neurologic causes of seizures as

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described in a previous report.[10] During the time period of this study, our basic management plan of eclampsia remained the same except for certain changes to improve on our basic protocol. The regimen of intravenous magnesium sulfate was changed to increase the serum magnesium levels achieved during therapy. The current regimen consists of a 6 gm loading dose infused over 20 minutes, followed by a maintenance dose of 2 gm/hr. The administration of hydralazine by a continuous infusion method is no longer used because of the high incidence of fetal distress associated with that therapy. The current treatment of severe hypertension consists of the use of either bolus injections of 5 to 10 mg of hydralazine or bolus injections of 20 to 40 mg of labetalol. In January 1985 an obstetric intensive care unit was established at this hospital, and since then all cases of complicated eclampsia have been managed in this unit.

Results

During the study period there were 254 patients with eclampsia among 83,720 deliveries (1/330 deliveries). One hundred six (40%) of these patients had prenatal care at our clinics and 148 (60%) either were maternal transfers or had no prenatal care. Two hundred (79%) were black, 53 (21%) were white, and one was Asian. This racial distribution is similar to that of the general obstetric population at the Perinatal Center. The mean age was 18.5 years (range, 11 to 36 years), but 221 (87%) were younger than 25 years.

Table I summarizes the clinical findings in these patients at the time of convulsions. It is important to note that the classic triad used to diagnose preeclampsia either was absent or the symptoms were mildly abnormal in about 20% of these patients. In addition, ≤50% of the patients had either severe hypertension or significant proteinuria at time of convulsions. One hundred twenty-two patients (48%) had eclamptic convulsions while they were under medical supervision in a hospital. Ten of these patients had convulsions after hospitalization for mild preeclampsia despite good response, and an additional 20 patients had convulsions while being evaluated for preeclampsia in an admission area. Evaluations were being carried out in various local hospitals and in our hospital for possible admission of the patients. These patients were having repeat evaluation of blood pressure or urine protein testing. The mean time that the patients were in the unit during evaluation was 72 minutes. The remaining 92 patients who had convulsions during hospitalization did so for the following reasons: while receiving standard magnesium sulfate therapy, during the postpartum period (late onset), while receiving other anticonvulsive prophylaxis, or after failure to institute appropriate antiprophylaxis therapy either during or immediately after birth.

Table II summarizes the gestational ages at the time of convulsions. Fourteen patients (5.6%) had eclampsia during the midtrimester, and in six of them eclampsia developed before 21 weeks' gestation. Five of the 14 patients had essential chronic hypertension, but none of them had connective tissue or renal disease. In addition, none of the 14 had evidence of renal disease on subsequent follow-up.

The onset of convulsions occurred before delivery in 181 patients (71%) and after delivery in 73 (29%). Forty (55%) of the 73 patients with postpartum eclampsia developed convulsions ≥3 days after delivery (range, 3 to 22 days). Twenty-two of these patients had preeclampsia before delivery, during labor, or post partum. They received intravenous magnesium sulfate during labor and for a minimum of 24 hours post partum. There was clinical evidence of improvement in the preeclamptic process in all 22, yet convulsions developed either during hospitalization or a few days after discharge. The other 18 patients were normotensive during pregnancy and had normal postpartum blood pressures. They had sudden onset of severe preeclampsia or convulsions at home and then were readmitted to the hospital. Headaches, visual disturbances, or both of 1 to 4 days' duration were reported by all patients before the onset of convulsions. None of these patients had a history of seizure disorder, and no patient had neurologic deficits or seizures on follow-up.

Thirty-three patients (13%) had convulsions while receiving standard doses of magnesium sulfate for intrapartum or postpartum treatment of preeclampsia. Four patients were receiving the standard intramuscular regimen recommended by Pritchard et al.,[11] one patient was receiving intermittent bolus injections of magnesium sulfate, and 28 were receiving the continuous intravenous regimen. In addition, 36 (14.2%) of the 254 women with eclampsia had one or more convulsions after institution of magnesium sulfate. Thirty of the 36 remained free of seizures after an additional 2 to 4 gm intravenous bolus of magnesium sulfate, three responded to a short-acting barbiturate, one required an intravenous Pentothal drip, and two required muscular paralysis with intubation to control further seizures.

Thirty-two patients (13%) had convulsions while receiving multiple drug therapy to treat preeclampsia before, during, or after birth. The drugs used were diuretics, various antihypertensives, analgesics, sedatives, and anticonvulsants (phenobarbital, diazepam, phenytoin). These drugs were used either orally, intramuscularly, or intravenously. In addition, 12 of the women with eclampsia had further seizures after receiving various doses of phenobarbital, diazepam, or phenytoin. It is important to note that four of seven patients with eclampsia who were treated with large doses of phenytoin had subsequent convulsions within

4 hours of receiving phenytoin. The clinical characteristics of these 32 patients were not different from those of the other patients. The majority of them were managed at local hospitals and the medications were prescribed by their physicians or by consulting physicians (internists or neurologists). Serum phenobarbital levels were not available in patients receiving such therapy; however, all four patients with recurring seizures after administration of phenytoin had adequate serum phenytoin levels. All five patients with aspiration in this study and six of the eight with cardiorespiratory arrest received a combination of these medications. Moreover, several women in this group were delivered of babies who had significant neonatal morbidity (respiratory depression, apnea, shock, acidosis, hypotonia, and low Apgar scores).

Perinatal outcome. The 254 pregnancies resulted in 263 births (nine sets of twins). There were 16 stillbirths and 15 neonatal deaths for a total perinatal mortality of 11.8%. It is important to emphasize that in 21 of the 31 cases of perinatal death the infants had a birth weight <1000 gm with 10 being <500 gm. In addition, two of the stillbirths were due to congenital anomalies and three neonatal deaths were due to congenital infections. Overall, the presence of abruptio placentae was associated with 12 of the 31 perinatal deaths.

One hundred twenty-four (49%) women had cesarean sections for various reasons. The most frequent indications were fetal distress, fetal growth retardation, abruptio placentae, extreme prematurity with unfavorable cervix, and failed induction of labor.

Maternal outcome. There was one maternal death (0.4%) in a patient with antepartum eclampsia at 39 weeks' gestation who was admitted in a moribund state. The patient had severe preeclampsia (blood pressure 220/140 mm Hg, 4+ proteinuria), yet she was transported in a private car and had several convulsions resulting in cardiac arrest at the time of arrival to the perinatal center. She was resuscitated and underwent cesarean section for management of fetal distress with delivery of a live term infant with good Apgar scores. The patient was comatose on admission and had a "silent" electroencephalogram immediately post partum that persisted until death 9 weeks later. Table III summarizes significant maternal complications in these patients. The incidence of abruptio placentae was 9.8%, but most of these complications occurred in patients with eclampsia before delivery. The incidence of the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) was also 9.8%, which was similar to the incidence seen in severe preeclampsia at our hospital.

Eleven of the 12 patients with acute renal failure had reversible acute tubular necrosis with six requiring dialysis. The average number of dialysis procedures per patient was 1.9 (range 1 to 4) and the average duration of oliguria-anuria was 4.6 days. All 11 patients had normal renal function on follow-up, including the patient who died (serum creatinine 0.5 mg/dl before death). The other patient had renal disease with significant renal impairment before pregnancy and required dialysis several months post partum. All 11 patients with pulmonary edema had multiple obstetric, medical, and, surgical complications requiring various therapeutic interventions.

A summary of all neurologic abnormalities is presented in Table IV. Except for the patient who died of diffuse cerebral encephalopathy, all neurologic abnormalities were transient without any residual deficit. Most of them were due to either cerebral edema, vasospasm, or infarcts. None of the patients had evidence of intracerebral hemorrhage. In addition, none of the surviving women had evidence of neurologic deficit or seizures on follow-up.

Table I. Clinical findings ($N = 254$)

	No.	*%*
Hypertension		
Severe	114	45
Mild-to-moderate*	82	32
Minimal or relative†	58	23
Proteinuria (0-trace)		
Absent	49	19
Significant (≤2+)	127	50
Edema		
Absent	80	32
Generalized	55	22

*Blood pressure between 140 and 160 mm Hg systolic and 90 and 110 mm Hg diastolic.

†Blood pressure ≤140 mm Hg systolic or ≤90 mm Hg diastolic.

Table II. Gestational age at onset of convulsions ($N = 254$)

Weeks' gestation	*Total cases*		*No. of postpartum cases*
	No.	*%*	
≤20	6	2.4	0
21-26	8	3.2	1
27-36	125	49.2	32
37-41	115	45.2	40

Comment

The findings of this study support our previous observation that the incidence of eclampsia in this hospital has not changed during the past 30 years.[7] This high incidence reflects the nature of the perinatal center that serves as the main referral center for many hospitals in five different states in the region. If one considers

Table III. Maternal complications ($N = 254$)

	Total cases		*No. delivered by cesarean section*
	No.	*%*	
HELLP syndrome*	25	9.8	20
Abruptio placentae	25	9.8	19
DIC†	13	5.1	9
Acute renal failure	12	4.7	9
Pulmonary edema	11	4.3	8
Cardiorespiratory arrest	8	3.1	6
Aspiration	5	2.0	5
Maternal death	1	0.4	

*Hemolysis, elevated liver enzymes, low platelets.
†*DIC*, Disseminated intravascular coagulopathy.

Table IV. Neurologic abnormalities ($N = 254$)

	No.	*%*
Transient deficit	8	3.2
Transient cortical blindness	6	2.4
Retinal detachment	2	0.8
Postpartum psychosis	2	0.8
Comatose state	3	1.2
Cerebral death	1	0.4
Intracerebral hemorrhage	0	0

the number of deliveries in the region and assumes that all women with eclampsia are referred to this center, the incidence of eclampsia for the whole region is about 1 in 1600 deliveries. This incidence is consistent with the national average and is similar to the respective incidence in the developed countries.

It is generally accepted that pregnancy-induced hypertension has an insidious onset with hypertension appearing relatively late in its course. The hypertension may be absolute (≥140/90 mm Hg on two separate occasions, at least 6 hours apart) or relative in the form of a threshold increase in either systolic or diastolic blood pressure. The diagnosis of preeclampsia requires the presence of hypertension with either edema, proteinuria, or both. It is also suggested that the clinical course in the development of eclampsia is characterized by a chronic, gradual process that begins with progressive weight gain followed by hypertension and proteinuria and ends with the onset of generalized convulsions or coma. The findings of this study reveal that a large percentage of patients with eclampsia lacked one or more of these clinical findings at onset of convulsions. In fact, 23% had minimal to absent hypertension, 19% did not have proteinuria, and 32% did not have edema. Overall, about 20% of these patients did not have the classic triad of edema, proteinuria, and hypertension. In addition, about one third of the women who had regular and appropriate prenatal care had abrupt onset of either severe preeclampsia or eclampsia.[7] None of these patients had any evidence of abnormal weight gain, edema, proteinuria, or changes in blood pressure. This finding is similar to that reported from Sweden by Moller and Lindmark[3] and to that reported from Scotland by Campbell and Templeton.[12]

There are several other clinical changes that might serve as warning symptoms before the onset of convulsions. These include severe and persistent headache, blurred vision, photophobia, irritability, transient mental changes, epigastric or right upper-quadrant pain, nausea, and vomiting. Some of these changes may be subtle, especially in the absence of significant hypertension or proteinuria, and may be missed by the nurse or physician during routine prenatal visits. Thus it is important that all health professionals taking care of pregnant women be familiar with the clinical changes that might herald the onset of convulsions. It is my opinion that all obstetric patients should be instructed to report the above changes immediately. In addition, these patients should be evaluated as soon as possible with prompt hospitalization of all patients with diagnosed preeclampsia. If the patient becomes normotensive in the absence of proteinuria and other premonitory symptoms, outpatient observation can be considered in a select group of patients. This form of ambulatory management is appropriate in reliable patients only during the early stages of the disease when the fetus is immature. These patients should be instructed to be at bed rest at home and to have frequent evaluation of blood pressure and urine dipstick measurements of protein. In addition, they should be evaluated by a physician at least twice a week.

Eclamptic convulsions may develop at home, at prenatal clinics, during maternal transport, during evaluation for preeclampsia before hospitalization, or during hospitalization for preeclampsia. It is disturbing to note that 48% of the women in this study had convulsions while under medical and nursing supervision. In some of these latter patients convulsions developed in the evaluation area during repeat measurements in cases of mild hypertension for establishing the diagnosis of preeclampsia or before admission to the labor and delivery area. One such patient developed a stormy course that was complicated by coma as a result of massive cerebral edema and by acute renal failure, liver failure, disseminated intravascular coagulopathy, and pulmonary edema. Fortunately, both mother and baby survived without any residual deficit. This finding underscores the importance of immediate hospitalization and prompt institution of magnesium sulfate therapy in patients presenting with any of the prodromal symptoms mentioned previously irrespective of the level of hypertension.

In several patients convulsions developed after hospitalization for preeclampsia. In some of them ante-

partum convulsions developed during conservative management of preeclampsia remote from term. These patients had convulsions despite being normotensive after hospitalization or while receiving various antihypertensive drugs and/or anticonvulsive oral medications. This finding is in disagreement with the recommendation that treatment of maternal blood pressure in preeclampsia will prevent eclamptic convulsions.[12] In addition, the use of oral anticonvulsive drugs such as diazepam, phenobarbital, or phenytoin in patients with preeclampsia does not prevent eclamptic convulsions and might give the clinician a false sense of security.

Seventy-nine patients (31%) had atypical onset of convulsions. In 33 convulsions developed while they were receiving standard regimens of magnesium sulfate; they developed in six at ≤20 weeks' gestation and in 40 at ≥3 days post partum. It is important to note that each of the 18 patients with normotensive gestations who experienced late-onset postpartum eclampsia had premonitory findings (headache or visual symptoms). In addition, 36 (14%) of the patients with eclampsia had subsequent seizures after receiving magnesium sulfate. Furthermore, several patients had subsequent seizures after receiving various other traditional anticonvulsive medications. These findings emphasize the need for close monitoring of all women with preeclampsia and eclampsia during labor and throughout the postpartum period. It is important to note that magnesium sulfate ultimately controlled eclamptic convulsions in 248 (98%) of the 254 women with eclampsia. Thus magnesium sulfate should remain the drug of choice to prevent and treat eclamptic convulsions.

Many obstetric units have little or no experience regarding the management of eclampsia. Consequently, most physicians are referring such patients, especially complicated cases and those remote from term, to tertiary care centers. Thus it is recommended that physicians and nurses referring such patients should consult with physicians at the perinatal center before transport, the patient should be stabilized regarding blood pressure and control of convulsions before transport, and the patient should be sent in an ambulance with medical personnel in attendance.

Pregnancies complicated by eclampsia are associated with poor maternal and perinatal outcomes. The reported maternal mortality ranges from 0.4% to 14% depending on the experience and facilities of the reporting center, as well as on the condition of the patient on admission to the center. Pritchard et al.[11] reported one maternal death among 245 women with eclampsia treated with a standardized protocol from 1955 to 1983. In addition, maternal morbidity was infrequent, and none of the patients had intracerebral hemorrhage. This excellent maternal outcome is attributed to the experience of the physicians managing these patients, the use of a standardized protocol for eclampsia, and the availability of appropriate intensive care facilities. In contrast, Lopez-Llera[14] reported 98 maternal deaths (13.9%) among 704 cases of eclampsia managed in Mexico, while Adetoro[15] reported 94 maternal deaths (14.4%) among 651 cases of eclampsia managed in Nigeria. However, it is important to note that many patients in these studies were admitted in a moribund state with multiple complications including intracerebral hemorrhage and cardiorespiratory, liver, and renal failure. There was one maternal death in this study that could have been prevented by proper maternal transport. In addition, many other patients had life-threatening complications caused by errors in management before and during transport. However, almost all of these patients survived without residual damage after arrival to the perinatal center. This finding emphasizes the importance of early and proper referral of such patients to centers with appropriate maternal and neonatal care facilities.

In summary, maternal mortality and morbidity in eclampsia are principally associated with complicated cases. Recent advances in both obstetric and neonatal intensive care have resulted in significant improvement in maternal and perinatal outcome of these pregnancies. Perinatal mortality and morbidity are mainly associated with abruptio placentae and eclampsia remote from term, especially in the midtrimester. At present, patients with these complications should be referred to a tertiary care center with the experience and facilities to manage critical maternal complications and provide intensive care for the immature infant.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Thomas M. Stubbs, Charleston, South Carolina (Official Guest). The disease eclampsia continues to threaten our patients, even as we enter the last decade of the twentieth century. In this large report of 254 cases, the sixth of a series, Dr. Sibai has shown five things of particular importance. First, we must beware of this disease, even in patients who lack either abnormal edema or abnormal proteinuria. Second, great caution is required in the presence of central nervous system symptoms, even when other findings indicate only mild disease. Third, magnesium sulfate continues to be associated with the best outcomes. Fourth, transport of the patient is a dangerous time. Fifth, good communications are important if there is a change of physicians. There are some differences in our management of these patients at the Medical University of South Carolina. We have had success with a continuous intravenous infusion of hydralazine for the control of severe hypertension. Whether one gives this drug as a series of small intravenous boluses, as is done in Memphis, or as a continuous intravenous infusion, as is done in Charleston, the pitfall for the physician is the same. That pitfall is the fact that the drug doesn't reach its peak effect until 20 minutes after administration. Thus overzealous dosing can result in a greater fall in blood pressure than was originally intended. Also, stress headaches are common in our patients, including those who go on to have preeclampsia. The physician at the bedside must use clinical judgment in deciding whether a particular headache is a signal for magnesium sulfate therapy. Nonetheless, these data do show convincingly that the physician should consider a headache a major threat in a patient with preeclampsia. The low incidence of maternal complications in this report is remarkable. Six years ago, Dr. Jack Pritchard published a series of 245 cases of eclampsia with only a single maternal death and no maternal intracranial hemorrhages; these maternal outcomes are identical to those presented here. Dr. Sibai has shown again that in the most experienced hands only an occasional maternal death will occur. Even so, this article reports no decrease in the incidence of eclampsia over the past 30 years at Dr. Sibai's institution. As we look to the future and as we look for a way to improve outcomes, the perils of maternal transport require our attention. Perhaps the most important finding in this article is that remaining maternal morbidity and mortality are so frequently linked to this transport problem. Dr. Sibai, how do you advise your colleagues in the Mississippi Valley regarding transport of patients with preeclampsia and eclampsia, including type of vehicle, accompanying personnel, drug choice, and route of drug administration? Also, do a patient's reflexes or a great distance from the hospital affect your advice regarding magnesium sulfate?

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Dr. Hugh Randall, Atlanta, Georgia. I can't tell you how much I enjoyed the article. It is always an enlightening event when Dr. Sibai presents the great work that he has done in hypertension. We have seen a number of complications occurring when the patient goes for imaging, either computerized tomographic imaging or magnetic resonance imaging, particularly when the patient goes directly from the intensive care unit to the radiology department. Dr. Sibai, what type of monitoring would you recommend when patients undergo imaging and at what stage of the disease would you recommend that imaging be done?

Dr. Sibai (Closing). I thank Dr. Stubbs for his comments. I guess the key issue is maternal transport. It has been a problem, and it continues to be a problem. Actually 2 weeks ago we had new memos and letters handed down to all physicians and nurses in the region suggesting to them the proper way to send these patients. It makes sense that when someone refers a patient to you he will call. We still have physicians and nurses who will send patients to us without even telling us the patient is on her way. At the present time, when a physician or nurse calls us, the first thing we tell them is that it is their responsibility to stabilize the patient before sending her. Some patients have a long way to go. If the patient is seriously sick, the referring doctor must take care of her even if she is in a local level I or level II hospital. We recommend that every patient receive magnesium sulfate irrespective of the severity of the disease. We recommend the use of 4 gm of magnesium sulfate intravenously plus 10 gm intramuscularly. If physicians don't like to use intramuscular magnesium sulfate, we recommend to them that they give a 6 gm intravenous loading dose plus 4 gm intravenous magnesium sulfate in 250 ml of fluid to be administered

over 2 hours. If this 4 gm is injected rapidly, it will not be toxic to the patient because the total will be 10 gm, which is safe for any patient who is pregnant. If the patient has severe hypertension, we recommend to the physician that they should control the blood pressure of the patient before sending her. The patient should be sent in an ambulance because, despite the intravenous magnesium sulfate, patients can still have convulsions. More important, we tell them to send an accompanying physician or nurse capable of handling her problems.

In regard to Dr. Randall's comments regarding computerized tomographic scans and magnetic resonance imaging, I have been doing them for research purposes. Some patients will lapse into coma, and some have more complicated cases of eclampsia, especially those that develop >3 days after delivery. In these cases the presence of other neurologic problems must be ruled out, and we would recommend doing computerized tomographic scan or magnetic resonance imaging. When do we send the patients for radiologic examination? Again, the patient has to be in a stabilized condition. Patients who have already received magnesium sulfate and patients whose blood pressure already has been controlled should be accompanied to the radiology department by faculty or a senior resident, who should be prepared to administer more magnesium sulfate or to perform emergency intubation.

Experience with the EndoPap device for the cytologic detection of uterine cancer and its precursors: A comparison of the EndoPap with fractional curettage or hysterectomy

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Cytologic assessment of the endometrium with the EndoPap sampler was compared with curettage or hysterectomy in 249 women with symptoms. The sensitivities for the detection of primary corpus cancer and hyperplasia were 0.90 (59/66) and 0.58 (18/31), respectively. All six cases of atypical endometrial hyperplasia were detected by the EndoPap device. Malignant EndoPap cytologic findings were present in 4 of 10 patients with a primary adnexal malignancy and normal endometrial histologic findings. Ninety-two percent of primary uterine cervical cancers were detected by EndoPap cytologic sampling. The specificity for the cytologic diagnosis of benign conditions was 0.93. EndoPap cytologic sampling has a reasonably high sensitivity for the detection of uterine cancers and preinvasive endometrial lesions with a high risk of progression to carcinoma. Further evaluation as to its usefulness in a screening program for uterine and adnexal cancers in postmenopausal women should be considered. (Am J Obstet Gynecol 1990;163: 1055-60.)

Key words: Endometrial cytology, uterine cancer

Endometrial cytologic sampling has lagged behind cervical cytologic sampling in its application and, most important, its impact on clinical practice. It is well known that the decline in the incidence of invasive cervical carcinoma has been primarily attributed to the widespread application of a cervical cytology screening program. A similar phenomenon has not occurred for endometrial carcinoma. Reasons for this are primarily because of the lack of an effective, inexpensive, and easy-to-use sampling method. In addition, greater expertise is needed to accurately interpret endometrial cytologic specimens, which frequently are unavailable on a routine clinical basis.[1] The EndoPap endometrial

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Fig. 1. EndoPap endometrial cytology sampler, Sherwood Medical Laboratories, St. Louis, Mo.

cytologic sampler (Fig. 1) was developed as an inexpensive and simple device aimed at improving the detection of endometrial cancer through routine screening. Palermo et al.[1, 2] have previously published their experience with the EndoPap sampler and found that it was easy to use with little to no patient discomfort reported. Few reports exist that correlate endometrial cytologic specimens with histologic specimens obtained at curettage or hysterectomy.[3] We report our experience with the EndoPap device and compare cytologic accuracy versus histopathology in women with symptoms undergoing uterine curettage or hysterectomy.

Material and methods

The study was approved by the research and ethics committee on human experimentation of all three institutions participating.

The EndoPap sampler was used to sample the endometrium of 249 women, ages 40 years or more (67% >50 years), before endometrial curettage or hysterectomy while under general anesthesia. The indications for curettage or hysterectomy are noted in Table I. Twenty specimens were obtained at Tampa General Hospital, 126 at the H. Lee Moffitt Cancer Center and Research Institute, and 103 at Bayfront Medical Center. Women with previous endometrial biopsies within the preceding 1 week or prior radiation therapy were excluded from the study. EndoPap samples were taken primarily by resident housestaff under the supervision of the authors (J.P.L., C.M., J.V.F., M.S.H., W.S.R., D.C.). For most patients, the EndoPap device was inserted directly through the endocervical canal without prior dilatation into the endometrial cavity. The device contains six hooklets (three anteriorly and three posteriorly) near the tip that collect uterine cells and tissue microfragments as it scraped over the endometrial/endocervical surface. Four to five strokes of the device were applied to both the anterior and posterior uterine surfaces. After the sampler was withdrawn, the specimen was smeared on glass slides in a manner similar to that used for cervical Papanicolaou smears and then immediately fixed by immersion in 95% ethyl alcohol. The cytologic smears were screened at each institution by cytotechnologists, and the final interpretation was made by one of the authors (S.N.-H.L.M., C.S.-B.M.C., and E.R.-T.G.H.). Clinical information and histologic diagnosis were restricted from the cytopathologist. The tissue report was considered the definitive diagnosis. Of the 249 patients evaluated, 38 had uterine curettage and 211 had hysterectomy after cytologic sampling. Eight patients had smears that were unsatisfactory because of insufficient cellularity or improper fixation, leaving 241 (96%) with adequate cytologic specimens.

Cytologic criteria. Tissue fragments obtained by EndoPap sampling included the following: (1) surface epithelial sheets, (2) gland segments, (3) stromal aggregates, and (4) variable endocervical tissue. Surface epithelial sheets appeared as flat or folded monolayers with sharp edges, occasional glandular opening or ostia, and evenly spaced nuclei containing micronucleoli. Gland segments appeared as tubular fragments of various lengths with irregular or rounded ends and were composed of monolayered epithelium with evenly spaced nuclei and micronucleoli. Stromal aggregates were identified as loosely cohesive groups with indistinct cell borders and round, oval, or bean-shaped nuclei usually containing a single micronucleolus. Endocervical tissue fragments represented a frequent contaminant of EndoPap samples and were distinguished from endometrial tissues on the basis of smaller size and the presence of larger, palisading cells, with larger nuclei frequently displaying characteristic protrusions of nipples.[4]

EndoPap samples were stained by the Papanicolaou method. In the early phase of this study, a cytologic classification of atypical endometrial cells was given to a few samples if cellular findings revealed nuclear enlargement with increased nuclear cytoplasmic ratio, nuclear hyperchromasia, and focal or irregular distribution of chromatin particles as reported as Cherkis et al.[5] Later, samples were divided into the following diagnostic groups: (1) normal, (2) consistent with endometrial hyperplasia, (3) consistent with endometrial hyperplasia with atypia, (4) consistent with endometrial adenocarcinoma or other specified uterine or extrauterine malignancies (i.e., endocervical adenocarcinoma or cervical squamous cell carcinoma). Criteria for assigning endometrial samples to each diagnostic group

were those of Palermo,[1] Meisels and Jolicoeur,[6] Ayer et al.,[7] and Massoni and Hajdu.[8]

The statistics presented are also generated from the group of 241 patients with adequate cytologic specimens. "Sensitivity," the ability to detect disease, was calculated by dividing the true positive by the total number of patients with corpus malignancy or endometrial hyperplasia and multiplying by 100. "Specificity," the ability to determine the actual percentage of disease-free patients, was calculated by dividing the number of true negatives by the total number of patients who did not have carcinoma or endometrial hyperplasia and multiplying by 100.[9]

Results

In 249 women undergoing EndoPap sampling, 13 (5%) required cervical dilatation before sampling because of cervical stenosis. Of the 241 patients with satisfactory EndoPap cytologic specimens, 66 patients had a positive tissue diagnosis of corpus malignancy, and 59 (0.90) cases were detected by cytologic study. In seven the cytologic findings were normal. The reasons for false negativity included cancer within a small polyp (two), small focal carcinoma (<1 cm, two patients), and sampling error (three).

Thirty-one patients had endometrial hyperplasia established by tissue diagnosis, and 18 cases were detected by abnormal cytologic findings (sensitivity, 0.58). All six women with atypical endometrial hyperplasia had abnormal endometrial cytologic findings. Abnormal EndoPap cytologic studies were noted in 13 of 19 patients with adnexal malignancies who had no symptoms of uterine disease. Nine had concomitant endometrial disease (endometrial hyperplasia, seven, cancer, two). In the remaining 10 patients, 4 (3 Stage IC or greater; 1 Stage IA) had malignant EndoPap cytologic findings with benign endometrium on histopathologic examination. Twenty-three of 25 cancers of the uterine cervix were detected by EndoPap cytologic sampling.

Of 109 patients with histologically normal endometrial samples obtained by curettage or hysterectomy and no gynecologic malignancy or hyperplasia, the cytologic diagnosis of the endometrial state was abnormal in eight patients, consisting of atypical endometrial cells or hyperplasia. Although atypical reactive endocervical cells were noted in 13 patients with a benign diagnosis, this finding was not considered a false-positive diagnosis of the endometrial state. The specificity of cytologic diagnosis for the benign endometrial state was 0.93 (101/109) (Table II).

Comment

Before the establishment of a screening program for uterine malignancies, the screening device must be carefully evaluated. In addition to providing an adequate specimen, the screening device must be easy to use (requiring little to no other instrumentation) and have a high likelihood of achieving successful insertion within the uterine cavity. In the present series the EndoPap sampler had a 95% successful rate of insertion without the need for cervical dilatation. In a previous study by Meisels et al.[10] in which the EndoPap sampler was used in an outpatient setting, uterine insertion was unsuccessful in 10% because of cervical stenosis. The device's small diameter of 2.0 mm facilitates successful insertion into the uterine cavity, particularly in comparison with other samplers with larger external diameters. This is especially important for postmenopausal patients, who have a higher incidence of cancer of the upper genital tract and in whom atrophic cervical stenosis is not uncommon.

Four percent (8/249) of the EndoPap samples were considered inadequate for cytologic diagnosis because of air drying artifacts or insufficient cellular specimens. On the basis of their experience with various endometrial samplers, Iversen and Segadal[11] reported that adequate endometrial samples were obtained more often on cytologic examination than after curettage in the postmenopausal patient with atrophic endometrium. The low rates of inadequate or unsatisfactory smears observed in our study and by others serve to enhance the cost-effectiveness of the use of endometrial cytologic sampling when applied to a screening program for uterine cancer, especially in postmenopausal women.[2, 9, 12-17]

EndoPap cytologic findings were abnormal in 90% of our patients with corpus cancer. In 10 patients the cytologic diagnosis, although less than malignant, would have directed the clinician to perform curettage to rule out the presence of malignancy. The EndoPap sampler method achieves a sensitivity for the detection of corpus cancer comparable with other incompletely controlled studies that use endometrial cytology instruments with differing methods of cell collection (Table III). EndoPap cytologic findings were falsely negative in 10% of corpus malignancies. Although focality

Table I. Indications for curettage or hysterectomy

Preoperative diagnosis	*N*
Peri/postmenopausal bleeding	40
Pelvic mass	63
Dysfunctional uterine bleeding	35
Endometrial hyperplasia	8
Cervical dysplasia	17
Vaginal carcinoma	2
Vulvar carcinoma	2
Cervical carcinoma	20
Endometrial cancer	60
Ovarian neoplasm	1
Chronic pelvic pain	1
TOTAL	249

Table II. EndoPap sampler: Comparative results of cytologic and histologic findings

Histologic diagnosis	*No.*	*Cytologic diagnosis*					
		Unsatisfactory	*Normal*	*Atypical*	*Hyperplasia*	*Hyperplasia with atypia*	*Suspicious for or frank malignancy*
Corpus cancer	67	1	7	1	8	1	49
Hyperplasia	25	—	13*	2	10	—	—
Atypical hyperplasia	6	—	—	—	3	2	1
Cervical cancer							
Squamous	17	—	2†	—	—	—	15
Adenocarcinoma	8	—	—	—	—	—	8
Ovarian/fallopian tube cancer‡	11	1	6	—	—	—	4
Benign/other	115	6	101§	4	4	—	—
TOTAL	249	—	—	—	—	—	—

*Includes two patients with endocervical glandular atypia.
†Includes one patient with reactive endocervical atypia.
‡Patients with benign uterine diagnosis only.
§Includes 13 patients with reactive endocervical atypia.

Table III. Sensitivity of the endometrial cytologic sampler for the detection of corpus cancer

Author	*Method*	*No. corpus cancers*	*Sensitivity (%)*	*Histologic diagnosis based on*
Regan and Sommerville[12]	Aspiration	20	90	C/H
Gravlee[13]	Lavage	53	100	C
Butler et al.[14]	Brush	6	100	C/H
Isaacs and Wilhoite[15]	Aspiration	7	86	C/H
Segadal and Iversen[16] et al.	Dislodgment	23	91	C
Palermo[2] et al.	Dislodgment	32	94	C/H
Bouchardy[17]	Aspiration	90	98	C/H
Bistoletti[3]	Dislodgment	34	97	C
Our series	Dislodgment	66	90	C/H

C, Curettage; *H*, hysterectomy.

of lesion was the main reason, a few more diffuse lesions were not detected. However, even uterine curettage has been reported to overlook endometrial lesions in as many as 10% of patients in whom curettage preceded hysterectomy.[18]

Endometrial hyperplasia was more difficult to distinguish from normal endometrium than was carcinoma by EndoPap cytologic sampling. The sensitivity of cytologic sampling for the detection of endometrial hyperplasia has long been recognized to be low. In a previous report, Palermo et al.[2] noted that the sensitivity for cytologic detection of endometrial hyperplasia was only 32%. Meisels and Jolicoeur[6] have published morphologic criteria for the cytologic assessment of hyperplasia and reported a sensitivity of 52%. Using similar criteria our overall sensitivity for the detection of hyperplasia was comparable. Our false-negative results were often associated with lower-grade hyperplasias. To improve the cytologic accuracy for the detection of low-grade hyperplasias, further research into improving morphologic cytologic criteria will be necessary.

Malignant EndoPap cytologic specimens were obtained in 4 of 10 patients with adnexal malignancies but normal endometrial pathologic findings. In evaluating the adnexal mass in postmenopausal women, Finkler et al.[19] have shown that the addition of sonography and serum tumor markers has provided better discrimination for predicting the presence of a malignant ovarian neoplasm than does physical examination alone. Our findings suggest that the addition of endometrial cytologic sampling may provide further discriminatory value in differentiating benign from malignant adnexal masses.

Currently within the United States based on American Cancer Society statistics, cancer of the uterine corpus is the most common malignancy of the female genital tract, followed by ovarian and cervical cancers.[20] Although corpus and ovarian cancer occur primarily

in postmenopausal women, cervical carcinoma is certainly not uncommon in the postmenopausal age group. According to Piver,[21] about 25% of all cervical carcinomas are in postmenopausal women, with 40% of the expected 7000 annual deaths occurring in this age group. Based on current American Cancer Society guidelines, the frequency of screening cervical cytologic samples is left to the discretion of the physician after a woman has had three adequate normal cervical Papanicolaou smears.[20] After three normal smears, there are currently no established or widely accepted guidelines to screen for cancer of the female genital tract. Debate currently exists regarding the value and effectiveness of endometrial sampling for screening women without symptoms for corpus neoplasms, and no technique of proven value is available to screen for the early detection of ovarian cancer.[22, 23] Despite the lack of universally acceptable guidelines, many clinicians continue to perform annual pelvic examinations and cervical Papanicolaou smears in postmenopausal women, recognizing the higher risk of malignancies of the upper genital tract in this age group. On the basis of our experience and previous reports, we suggest that the EndoPap sampler undergo further evaluation regarding its usefulness in a screening program for the detection of uterine and adnexal cancers in postmenopausal women.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. BENEDICT B. BENIGNO, Atlanta, Georgia (Official Guest). The incidence of endometrial carcinoma in the United States is more than twice that of cervical carcinoma (36,000 vs 14,000), a reversal of the ratio seen a generation ago. The incidence rate of 21.1/100,000 with a lifetime risk of 2.4%, making this the most common gynecologic malignancy. Only the risks of carcinoma of the breast (9.0%) and colorectal cancer (5.7%) are greater.[1]

The vast majority of these neoplasms are diagnosed after tissue sampling of the endometrium because of postmenopausal bleeding. The only cytologic screening procedure at the time of the annual pelvic examination for thse patients remains the traditional Papanicolaou smear, even though it has been known for many years that such cytologic sampling will miss about 50% of endometrial cancers. The incidence of poor prognostic parameters such as high-grade histology, deep myometrial invasion, and nodal metastasis is significant, and one cannot help but wonder about the extent to which routine endometrial screening might one day diminish such parameters.

The ideal screening procedure should be safe, painless, easy to perform, and highly reliable. It is unfortunate that the patients presented in this series had the endometrium sampled under general anesthesia. Not

only can no comment be made regarding the pain associated with this procedure, but it is possible that a more representative tissue sample was obtained because the patient was not awake. Despite the fact that the samples were obtained under anesthesia, the EndoPap device had only a 90% sensitivity for the detection of corpus cancer, which was the second lowest in the series presented in Table III.

This device had the same high failure rate with respect to endometrial hyperplasia (13/31) as is reported in most other series, but it is encouraging to note that all six cases of atypical endometrial hyperplasia were detected. The incidence of cancer was more than twice that of endometrial hyperplasia, but this is most likely because this study investigated the endometrial cytology of patients with serious pelvic disease and was not designed as a screening study.

It was very gratifying to see that 13 of 19 patients with an adnexal cancer had positive endometrial cytologic findings, and of these 19 patients, only two had a concomitant malignancy in the endometrium. Routine cytologic screening of the uterine cervix is virtually useless with respect to cancer of the ovary, and I doubt whether the use of serum CA 25 or pelvic ultrasound examination will have much of an impact as screening procedures for ovarian cancer.

It would appear that the detection of cancer of the ovary is not the only "bonus" in this study. In 23 of the 25 patients with carcinoma of the cervix, the EndoPap device detected the lesion. Although most cancers of the endocervix are easy to detect with the Papanicolaou smear and the colposcope, it is not uncommon for cancers beginning high in the endocervical canal to have a negative Papanicolaou smear and elude even the most experienced of colposcopists.

In Norway, Iversen and Segadel[2] used endometrial cytologic sampling as the first diagnostic procedure in the evaluation of patients with postmenopausal bleeding, which reduced the hospital curettage rate by 70%, a figure that they claim will eventually be as low as 90%. In the United States approximately 210,000 hospital curettages are performed each year for postmenopausal bleeding or for the screening of postmenopausal women. At an average cost of $1925, a 70% reduction would represent an annual savings of 283 million dollars.[3]

In this very fine and timely study, the authors call attention to the inadequacy of the annual pelvic examination and cervical Papanicolaou smear in the detection of malignancies of the upper genital tract. Rather than expand on this work in the form of a screening study as the authors have suggested, have we reached the point in which cytologic assessment of the endometrium should be part of the routine annual evaluation of postmenopausal patients?

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DR. LAPOLLA (Closing). I think we might be able to do a little bit better in our approach to postmenopausal patients than we are currently doing with the cervical Papanicolaou smear. An evaluation of our experience points out that the addition of office endometrial cytologic sampling may be of value in our screening approach to postmenopausal women. There are many issues with respect to screening patients for endometrial cancer that are not addressed in this study, and there are pros and cons for screening for endometrial cancer, which you will note in the literature. My point behind the use of office endometrial cytologic sampling is that it can be used for more than just screening for endometrial cancer. I tried to point out in the article that the incidence of invasive cancers of the upper genital tract, the cervix, uterus, and ovary, are fairly significant in the United States. You have to examine all three types of cancers in postmenopausal women and not just focus on endometrial cancer. Many noted authorities on this subject have proposed that endometrial cytologic sampling or screening not be used primarily, because the overall death risk for patients with endometrial cancer is really fairly low. I believe that it is better to look at the total picture of genital tract cancer in postmenopausal women. About 25% of all cervical cancers in the United States occur in postmenopausal women, and most women with ovarian cancer and endometrial cancer are postmenopause; thus I think you have to examine all three major types of malignancies of the upper genital tract in terms of screening. We cannot just focus on the issue of endometrial cancer.

Diagnosis and management of prenatally detected myelomeningocele: A preliminary report

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Our experience with 23 cases of fetal myelomeningocele provides preliminary information on the outcome of these infants diagnosed in utero and managed by a multidisciplinary team. The mean age of diagnosis was 23.7 weeks (range, 16 to 34 weeks). Mean gestational age at delivery was 36.9 weeks in the 14 patients who elected to continue their pregnancies. None of the 11 infants with lumbosacral or sacral lesions developed significant ventriculomegaly before term. Of the three patients diagnosed with thoracolumbar lesions, two had progression of ventriculomegaly necessitating early delivery at 32 to 34 weeks of gestation. These preliminary findings suggest that a coordinated prenatal and neonatal approach appears to result in a favorable prognosis for infants with myelomeningocele, but that neonatal complications are common, requiring careful monitoring and aggressive management. (AM J OBSTET GYNECOL 1990;163:1061-5.)

Key words: Myelomeningocele, prenatal diagnosis, spina bifida

The advent of high-resolution ultrasonography and the widespread implementation of maternal serum α-fetoprotein screening have led to a marked increase in the number of cases of spina bifida detected in utero. However, little information is available regarding the natural history and progression of prenatally detected myelomeningocele. We report the preliminary experience of an ongoing longitudinal evaluation of infants diagnosed in utero with myelomeningocele, who were managed both prenatally and postnatally by a multidisciplinary team.

Material and methods

From July 1, 1986, to Oct. 31, 1989, 23 patients were referred to the Prenatal Diagnosis and Treatment Center of the University of Virginia Health Sciences Center for the management of pregnancies complicated by fetal myelomeningocele. Each patient had an initial ultrasound examination to determine the size and level of the lesion, possible existence and degree of ventriculomegaly, and the presence of other fetal abnormalities. A fetal karyotype was obtained by either amniocentesis or percutaneous umbilical blood sampling in all patients.

On completion of the diagnostic evaluation, the family met separately with a geneticist and a developmental pediatrician for counseling regarding the findings in the fetus and their implications for neonatal management. Discussions also centered on the long-term prognosis of spina bifida in children with similar lesions. Options for pregnancy management, including pregnancy termination, if applicable, were discussed in a nondirective counseling fashion.

Patients who chose to continue their pregnancies were followed by serial ultrasound evaluations every 3 to 4 weeks. Delivery was performed by cesarean section when fetal lung maturity was attained or earlier if significant ventriculomegaly (cortical mantle thickness <10 mm) was documented. Each newborn infant had an initial examination to determine the level of the lesion, the level of neurologic deficit, and the presence of other malformations. Follow-up examinations and developmental testing was performed by a multidisciplinary team of developmental specialists at the Kluge Children's Rehabilitation Center of the University of Virginia, under the direction of one of the authors (S.A.D.).

In pregnancies in which termination was chosen, autopsies were performed in all cases to confirm the ultrasound findings. Postmortem radiographs were obtained in all cases.

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Table I. Comparison of continued versus electively interrupted pregnancies diagnosed with fetal myelomeningocele

Outcome (N)	*Mean gestational age Dx (range)*	*Level lesion*				*Other abnormalities*
		CER	*TL*	*LS*	*S*	
Cont (14)	26.6 (16-34)	0	3	7	4	2 (Unilateral renal agenesis, trisomy 9 mosaicism)
Inter (9)	19.4 (17-26)	1	5	3	0	1 (Horseshoe kidney)
OVERALL (23)	23.7 (16-34)	1	8	10	4	

Dx, Diagnosis; *CER,* cervical; *TL,* thoracolumbar; *LS,* lumbosacral; *S,* sacral; *Cont,* continued; *Inter,* electively interrupted.

Table II. Natural history of fetal myelomeningocele based on level of lesion

Level	*Total No. pts.*	*Ventriculomegaly*		*Gestational age at delivery (wk)*	*Postnatal shunting*
		Present	*Progression*		
Thoracolumbar	3	3	3	34.3*	3
Lumbosacral	7	7	0	37.9	7
Sacral	4	3	0	37.3	2
OVERALL	14	13	2	36.9	12

*Two patients electively delivered at 32 and 34 weeks, respectively, because of significant ventriculomegaly.

Results

The characteristics of continued pregnancies are compared with those of terminated pregnancies in Table I. For the total group the mean gestational age at diagnosis was 23.7 weeks, with a range of 16 to 34 weeks. The distribution of the level of the lesion and the incidence of associated abnormalities were similar in both groups. Neither of the renal malformations was detected on the initial sonogram. Of the 14 continued pregnancies, 13 had ventriculomegaly at the time of diagnosis; 9 of 12 terminated pregnancies had ventriculomegaly. No fetus in either group had significant enlargement of the ventricles at the time of initial diagnosis. However, the time of initial diagnosis was significantly earlier (7 weeks) in those patients choosing termination.

Table II provides an outline of the natural history of in utero–detected myelomeningocele. Of the 14 patients only 2 had progression to significant ventriculomegaly. Both fetuses had thoracolumbar lesions and were delivered at 32 and 34 weeks, respectively, because of the degree of ventricular enlargement. Of the remaining 12 patients, all were electively delivered when fetal lung maturity was documented except one, who delivered at 35 weeks after unsuccessful treatment for preterm labor. All fetuses with lesions above the sacral area required postnatal shunting for progressive ventriculomegaly despite the absence of progression in utero in 80% of the cases.

In Table III outcome criteria for surviving infants with at least 12 months of follow-up are depicted based on level of lesion. The cases are equally distributed in each category, and no striking differences are seen between groups. There are no cases of significant developmental delay in any category. Two of 10 infants required posterior fossa decompression because of episodes of apnea.

Apnea also contributed to the deaths of 2 of 14 study patients for a mortality rate of 14.3%. One death occurred in a 15-month-old child because of bowel necrosis after a prolonged apneic episode. A second child died at home at 1 month of age, presumably the result of an unrecognized apneic event.

Comment

In recent years a marked increase in the number of cases of prenatally detected myelomeningocele has been documented.[1, 2] Providing families with accurate information regarding the natural history and prognosis, however, has been limited to extrapolations made from data in which myelomeningocele was detected in newborn infants. Much of this published information also predates the significant advances made in neonatal intensive care.[3, 4] Obtaining longitudinal data at the time of in utero diagnosis and continuing through the first few years of life is essential for the counseling of families in whom a fetus with myelomeningocele is detected. In this report we present our preliminary information from a project undertaken to study the effects of a coordinated management approach, both

Table III. Prognosis of surviving infants based on level of lesion (12 months or greater follow-up)

Level	*Mean age (mo)*	*Total no. pts.*	*Bladder dysfunction*	*Development delay (mild)*	*Morbidity*
TL	26	3	3	1	0
LS	21	3	1	1	1*
S	21	4	3	2	1*
OVERALL	23	10	7	4	2

TL, Thoracolumbar; *LS*, lumbosacral; *S*, sacral.
*Required posterior fossa decompression for episodes of apnea.

prenatally and neonatally, on the outcome for children with myelomeningocele.

Although the number of cases to date is small, some interesting observations have been made. First, fetuses with lumbosacral or sacral lesions do not have a significant risk of progression of ventriculomegaly in utero. The finding was surprising in view of the fact that 10 of the 11 fetuses had enlarged ventricles at the time of diagnosis, and nine required postnatal shunting. In contrast, two of the three patients with thoracic lesions had progressive ventriculomegaly, which necessitated early delivery. However, the good outcome in both cases suggests that an aggressive management approach may be associated with a good prognosis for mental development. We recognize that bias may be introduced by the significantly later time of initial diagnosis in the group of pregnancies that were continued; however, the distribution of levels of lesion and the degree of ventriculomegaly were similar in both groups. Therefore the outcome in the continued pregnancies should accurately reflect that for the total group.

In 10 patients a mean postnatal observational time of 23 months has been completed, and the preliminary findings suggest that this coordinated prenatal and neonatal management results in a favorable prognosis. None of the infants have significant developmental delay. The mild delays seen in four patients are likely to be a reflection of the heavy weighting of the testing modalities on tasks that require normal lower motor function, skills not possible in these infants. Our data also support the assertions of Shurtleff et al.[4] and McLaughlin et al.[5] that infants diagnosed in utero and born without trauma have few contraindications to immediate surgical care, a factor that was shown in their studies to be associated improved outcome. Likewise, McLone[6] has documented similar survival rates and mental development in infants with the use of prompt surgical management.

However, neonatal complications are quite common and resulted in significant morbidity (2/10) and mortality (2/14) in the children followed for >12 months. Each of these occurrences appears to be directly related to apneic episodes. In the two surviving children, posterior fossa decompression resulted in resolution of the problem. These findings suggest that careful monitoring of these infants and aggressive management are an essential part of the long-term care of children with myelomeningocele.

The optimal mode of delivery for the infant with myelomeningocele is controversial. Chevernak et al.[2] suspected that cesarean section might be a potentially beneficial procedure based on their review of older literature that appeared to indicate a detrimental effect on neurologic outcome in infants delivered vaginally. More recently Benson et al.[7] reviewed retrospectively the records of 75 infants with open spina bifida. They found no significant difference in mortality, incidence of neonatal meningitis, or developmental status at 1 year of age between infants delivered vaginally and those delivered by cesarean section. However, interpretation of their data is difficult because of small numbers and because 40% of patients who had cesarean section had prior labor. In addition, the incidence of neonatal meningitis was quite high (4/72 infants), and three of these infants were in the vaginally delivered group. Infection of the central nervous system is known to be a limiting factor in the intelligence of children with myelomeningocele.[8] Elective cesarean section before labor provides an aseptic, atraumatic mode of delivery. Infants born in this manner have fewer contraindications to immediate surgical care, and there is the potential for a better outcome.[5] However, only carefully controlled, prospective clinical studies will provide the necessary data to resolve this management dilemma.

Our preliminary data indicate that the finding of a myelomeningocele in the fetus can be associated with a good prognosis. A coordinated management approach beginning at the time of diagnosis appears to enhance the potential for a favorable outcome. Further study is needed before more precise prognostic statements can be made.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Richard C. Taft, Greenville, North Carolina (official guest). Dr. Hogge and colleagues are to be commended for their endeavors to document the natural history of in utero–diagnosed meningomyelocele. They have confirmed that ventriculomegaly usually coexists with meningomyelocele at the time of diagnosis by sonography and that higher lesions are more likely to have progressive ventriculomegaly. Also atraumatic delivery at term by cesarean section is recommended. Interestingly, they report that 9 of 10 neonates required shunts despite no progression in utero. Perhaps this is a result of the now-aggressive neurosurgical approach at the time of delivery. McLaughlin et al.[1] report an increased frequency of surgical treatment in neonates once thought to have a poor prognosis. This approach allows the degree of injury to be halted at birth and therefore a more favorable long-term outcome.

Hogge et al. recommend intervention in infants with progressive ventriculomegaly, but the number of infants is small and he had no control group. Indeed, pediatricians debate the validity of using cortical mantle thickness as an accurate predictor of long-term development. I also find it interesting that infants with higher clinically, more significant lesions in the thoracic area, which supposedly have a graver long-term prognosis, were not in the group that developed the severe complication of brain-stem herniation.

As Dr. Hogge and colleagues continue this longitudinal study of neural tube defects, I would find it interesting if they could define a graphic correlation between the lateral ventricle/hemispheric width ratio and the severity of morbidity and mortality. Screening criteria also need to be established for neonates at risk for herniation because 25% of the infants in this study and that by Chevernak et al.[2] developed brain-stem compression. Perhaps in utero evaluation of fetal breathing movements or fetal bradycardia might identify this group of infants. Also, sonographic evaluation of the posterior fossa contents, such as cerebellar transverse diameter, might be helpful as an indicator.

I would also like Dr. Hogge to comment on the sonographic sign of angulation or pointing of the fetal frontal bone as an indicator of an associated neural tube defect as reported by Penso et al.[3] If confirmed, this sign will help all obstetricians who do anatomic surveys with sonography to diagnose meningomyeloceles more frequently.

In summary, the study of Hogge et al. demonstrates the importance of the multidisciplinary approach to a very severe developmental defect that in the past has always led to death or disability. Early prenatal diagnosis armed with the knowledge of the natural history of neural tube defects will allow parents to make informed decisions about continuing their pregnancy with hope or terminating when the prognosis is poor.

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Dr. Alfred H. Moffett Jr., Leesburg, Florida. As a clinician, I feel that this is a very important paper. I personally managed a case that emphasizes several points. First, it was followed by both the clinician and the academician. Second, the ultrasound diagnosis of fetal meningomyelocele led to delivery by cesarean section at 38 weeks' gestation. The infant was taken immediately to surgery by the pediatric neurosurgeon. That child now runs up and down the hallway in my office. I consider this the therapeutic triumph of my career. I really feel as though this is an entity that if found early, does give hope for successful treatment. How are the children doing with their subsequent development?

Dr. William Kirkley, Fort Lauderdale, Florida. I would like to ask Dr. Hogge if he reviewed Dr. Lorber's work in England on these children. About 12 years ago, he wrote a paper on this, in which he took a very aggressive surgical approach once the child had delivered. His conclusion after following these children for many years was that not one of them ever married successfully, and I do not think any of them were ever gainfully employed. His conclusions were "What have thou wrought?"

Dr. Hogge (Closing). I thank Dr. Taft for his excellent comments and confirm that we in fact found

the ultrasound findings to be very much as has been described. Most, if not all, of the infants who were diagnosed before 26 weeks had the frontal bone sign known as the lemon sign. Unfortunately, they also had the very small posterior fossa that can be seen by looking at the cerebellum. It was not helpful in terms of what infants would have difficulties in the neonatal period. There were also no findings on neonatal ultrasound examinations that were helpful in discriminating between those who would have apneic episodes and those who would not.

I will go to the last question first because I think it relates to all the questions that were asked; that is, what is the ultimate prognosis for these children? The ultimate prognosis for these children is very different in 1990 than it was at the time of Dr. Lorber's work. These children are now, as you are well aware, mainstreamed into school systems. They are also taken care of by multidisciplinary teams that help with the management in the areas of physical therapy, occupational therapy, and so forth, and there is no reason that these children cannot be gainfully employed. As is well known in the recent literature, the incidence of mental retardation is these children is quite low. It is higher than that in the general population but is significantly lower than seen at the time of Dr. Lorber's original work. There is no reason, other than being wheelchair bound in the cases of lesions above L-2, that these children should not grow up and be gainfully employed and be members of this organization for that matter.

These children are not running around in my office because they do in fact have significant neurologic lesions. In those children in whom the lesion is above L-2, they will be wheelchair bound. As you move down the spine from that point, we talk about braces. In some cases we expect those with the lower lumbar and sacral lesions to walk with the aid of braces, but in fact they should have a good outcome. We will present to you in another 6 years the data on these children when they are in school. We should then have a better idea of their ultimate prognosis at that point.

Outpatient obstetric management of women with type I diabetes

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Conventional obstetric management of diabetic women has frequently incurred extensive hospitalization. Although this approach improved perinatal results for these women and their infants, it is costly and cumbersome. The 3-year experience of an outpatient diabetic obstetric clinic is compared with the results obtained at the same facility during 5 previous years when hospitalization was used more extensively. Perinatal mortality and morbidity were not different in 51 type I diabetic women managed almost entirely as outpatients when compared with 58 similarly complicated diabetic patients receiving more conventional management. Mean prenatal admissions (1 vs 2, $p = <0.01$), mean prenatal hospital days (6 vs 12, $p = 0.05$), and prolonged delivery admissions of >7 days (31% vs 69%, $p = < 0.01$) were significantly less. Outpatient obstetric management of diabetic women efficiently decreases maternal morbidity without increasing infant morbidity and mortality. (Am J Obstet Gynecol 1990;163:1065-73.)

Key words: Outpatient care, type I diabetes, pregnancy

In diabetic pregnancies, management directed at improving fetal outcome has seldom been balanced by a corresponding effort to improve maternal morbidity. Maternal hospitalization, often extensive, is still considered a fundamental measure in the management of pregnant diabetic women.[1-3] Maternal hospitalization contributes to maternal morbidity. It does not improve perinatal morbidity or mortality.[4-6] Reported rates of cesarean section are high.[2-4, 7, 8]

Successful pregnancy in diabetic women is currently measured more often in infant morbidity and the incidence of congenital anomalies than in perinatal mortality. At least in settings offering intensive preg-

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Table I. Group characteristics

Characteristics	*Group A N (%)*	*Group B N (%)*	*Significance*
No./% of total	51(47)	58(53)	—
White classes A-D (No., % of group)	41(80)	53(91)	NS
Diabetic nephropathy (No., % of group)	10(20)	5(9)	NS
Age (mean)	(25)	(25)	NS
Parity (mean)	(1)	(1)	NS

Table II. Hemoglobin A_1 values (%) in 51 study group patients

Mean initial Hgb A_1	12.1 ± 2.1
Mean Delivery Hgb A_1	9.2 ± 2.3
Initial HgbA_1 <10%	9 (18%)
Delivery HgbA_1 <10%	31 (61%)

HgbA_1, Hemoglobin A_1.

nancy care, perinatal mortality rates have greatly improved.[1-3, 7, 9] Congenital anomalies remain a significant cause of fetal morbidity and mortality despite efforts directed at prevention.[10, 11] The incidence of infant morbidity unrelated to anomalies has decreased.[2, 3, 8, 12]

This study was undertaken in pregnant women with type I diabetes mellitus to determine the efficacy of outpatient management in reducing maternal morbidity without increasing perinatal morbidity and mortality.

Material and methods

In 1985 the University of Virginia Obstetrical Service organized an outpatient clinic for type I insulin-dependent diabetic women in an attempt to minimize hospitalization by providing comprehensive ambulatory care. Since then, 51 pregnancies have been managed in 47 women with type I diabetes mellitus (group A). The results of this project are compared with those of the preceding 5 years, when 58 pregnancies complicated by diabetes were managed by use of routine antepartum hospitalization (group B). Pregnancies in both groups complicated by spontaneous and elected abortion were not included in this analysis.

Throughout pregnancy, women were treated by an obstetric nurse trained in diabetic management, an attending obstetrician/internist, a resident assigned on a rotating basis, and a dietician. Initial visits for most women did not occur until late in the first trimester or early second trimester. Some women were not seen until the third trimester. Only one woman had counseling before a first pregnancy. Most women were rural and indigent, many lived at least 1 hour from the clinic, and only nine had medical insurance.

All were treated with combinations of intermediate- and short-acting or long- and short-acting insulin. Human insulin was used exclusively since 1986.

During the first year of the study, women were hospitalized for instruction if initiating insulin therapy, inexperienced with home glucose monitoring, or very poorly controlled. This practice was discontinued thereafter. All patients except one used home glucose monitoring. Glucose monitor readings were correlated with hospital laboratory glucose determinations. Patient contact by visit or telephone occurred as often as daily. Fasting, premeal, and bedtime glucose measurements were considered good at levels below 100 mg/dl at fasting and 120 mg/dl at other times. Hemoglobin A_1 determinations were made at the outset of care and subsequently every 2 months. These were done with an affinity chromatography method having an upper limit of normal of 7%. Clinical assessment of glucose control was made primarily on the basis of glucose measurements. Hemoglobin A_1 levels were used to verify glucose levels and in the analysis of data for this report.

All women had retinal evaluation by an ophthalmologist skilled in the assessment of retinal disease. Women with proliferative retinopathy or advanced benign retinopathy were assessed each month. Renal function was evaluated each trimester with 24-hour urine collection for creatinine clearance and total urinary protein. Urinalysis was done regularly to screen for infection. An electrocardiogram was done on all women with vascular disease.

An ultrasound examination was performed when possible at 16 to 20 weeks' gestation to screen for fetal anomalies and to confirm gestational age. Scans were repeated in the second trimester to evaluate growth. All had α-fetoprotein testing, and karyotyping was done on samples obtained by amniocentesis or chorionic villus sampling when justified by risk. Women seen initially at more advanced gestational age had ultrasound examinations as soon as they were seen and did not have α-fetoprotein testing.

Antepartum fetal testing was begun at 30 weeks' gestation in women with vascular disease, poor control, or special risk. They were tested weekly until 35 weeks' gestation and thereafter three to seven times a week until delivery. In others it was started at 32 weeks' gestation. In stable women without vascular disease, tests were done weekly until 37 weeks' gestation and three times each week thereafter. The nonstress test was primarily used, with contraction stress tests, biophysical profile and Doppler ultrasound studies reserved for situations in which the results of the nonstress were not reassuring.

Table III. Maternal morbidity

	Group A (N = 51)			*Group B (N = 58)*			
	No.	*%*	*Mean ± SD*	*No.*	*%*	*Mean ± SD*	*Significance*
Prenatal Admissions	52	—	1 ± 1	114	—	2 ± 1.3	$p = <0.01$
Prenatal hospital days	—	—	6 ± 8	—	—	12 ± 10	$p = <0.05$
<6 prenatal hospital days	40	78	—	19	33	—	$p = <0.01$
Prenatal hospitalizations limited to 1 or none	41	80	—	23	40	—	$p = <0.01$
Delivery hospitalizations >7 days	15	29	—	40	69	—	$p = <0.01$
Preeclampsia	3	6	—	13	22	—	$p = <0.01$
Cesarean section	26	50	—	26	45	—	NS
Endometritis	2	4	—	8	14	—	$p = <0.05$

When the induction of labor was planned, amniotic fluid was assayed for the lecithin/sphingomyelin ratio and phosphatidylglycerol to determine fetal pulmonary maturity. The fetus was considered mature when the ratio was 2 and phosphatidylglycerol was present. Women were allowed to go into spontaneous labor unless there were contraindications but had induction of labor at 40 weeks if undelivered otherwise by then. Some had earlier induction if the cervix were very favorable. They had amniocentesis for maturity studies. These women were admitted on the day of induction of labor, and blood glucose level was maintained at approximately 100 mg/dl with a continuous infusion of glucose and insulin.

All deliveries were attended by pediatricians, and infants were admitted according to need either to the normal newborn nursery or the intensive care unit. Infants were considered hypoglycemic when glucose levels were <45 mg/dl. Hyperbilirubinemia was diagnosed when bilirubin levels were >12 mg/dl.

Statistical analysis was performed by means of the Student *t* test, χ^2 analysis of variance, and Fisher's exact test.

Results

The 51 women in the outpatient study group (group A) did not differ from the 58 women treated more conventionally (group B) in age, parity, or White classification of diabetes (Table I). There were 41 women in the study group and 53 in the comparison group who were classified as B through D. The numbers in each class within groups were similar. Ten women in group A and five in group B had diabetic nephropathy. None had heart disease.

As shown in Table II, at initial evaluation, glucose control, as reflected by hemoglobin A_1, was poor in most study group women. Seven women had normal hemoglobin A_1 at presentation, and blood glucose values indicated good control. Nine women had a level of <10%. The mean for the group was 12%. By delivery, 31 women (61%) had hemoglobin A_1 levels of <10% and the mean had decreased to 9.2%. Near-normal levels (<8.5%) were obtained in 21 women (41%). Insufficient data exist to characterize glucose control accurately in group B women. However, with the exception of glucose meter use and emphasis on outpatient treatment, management methods and goals were similar.

Maternal morbidity. Initially the study objective was frustrated by the perceived need to hospitalize for the initiation of insulin therapy and glucose monitoring and also to redirect poorly controlled women. In later cases hospitalization was reserved for illness. Group A women were hospitalized less often and for shorter durations than previously treated women. The mean number of prenatal admissions was significantly less for group A women (Table III), and hospitalizations were more often limited to 6 days or less. Compared with earlier patients, twice as many in the study had either no confinement or only one and used half as many hospital days (6 vs 12, $p = < 0.05$) (Table III). In addition to regular antenatal admissions, prolonged admission for late pregnancy monitoring and delivery was common among women treated before the project. Delivery admissions >7 days were far more common in group B women that in those included in group A (69% vs 29% $p = < 0.01$).

Rates of cesarean section were the same in the two groups (group A 50% vs group B 45%, p = NS) (Table III). Endometritis after cesarean section was far more common in the earlier group. Preeclampsia was diagnosed significantly fewer times in group A women. No women in the study group had pyelonephritis. One woman in the study group required hospitalization for hypoglycemia. There were no instances of antenatal ketoacidosis. Data relating to the incidence of pyelonephritis and hypoglycemia in group B women were not examined.

Group A women with diabetic nephropathy are presented in Table IV. Seven had essentially normal newborn infants, and all 10 infants ultimately did well. Half were delivered by cesarean section, as was the case with

Table IV. Pregnancy results in women with renal disease

Patient No.	*EGA at delivery*	*Delivery*	*Maximum proteinuria (mg)*
1	32	C/S	10,000
2	34	C/S	15,659
3	37	SVD	6,792
4	37	SVD	1,085
5	34	SVD	4,578
6	36	SVD	2,485
7	35	C/S	11,552
8	38	C/S	8,000
9	37	SVD	8,000
10	34	C/S	10,703

*Hemoglobin A_1 at delivery.
EGA, Estimated gestational age; *C/S,* cesarean section; *SVD,* spontaneous vaginal deliveries.

Table V. Newborn morbidity and mortality

Characteristics	*Group A (N = 51)*		*Group B (n = 58)*		*P*	*95% Confidence interval*
	No.	*%*	*No.*	*%*		
Delivery at <38 wk	29	57	43	74	$p = <0.01$	
Required intensive care	12	23	17	29	NS	−0.19, 0.31
Neonatal hypoglycemia	12	23	13	22	NS	−0.24, 0.26
Neonatal hyperbilirubinemia	6	11	26	45	$p = <0.01$	
*Apgar score < 5 at 5 min	3	5	3	5	NS	−0.02, 0.02
†RDS	9	18	11	19	NS	−0.32, 0.34
Delivery weight >4000 gm	9	18	6	10	NS	−0.29, 0.13
Delivery weight <2500 gm	9	18	11	19	NS	−0.32, 0.34
‡†Anomaly	3	6	6	10	NS	0.07, 0.15
Mortalities	2	3.9	2	3.4	NS	−0.125, 0.135

RDS, Respiratory distress syndrome.
*Excludes cases of intrauterine death.
†‡Fisher's exact test.

the entire group. Four of the 10 pregnancies were complicated by hypertension, seven by renal excretory insufficiency, and all by significant proteinuria, massive in all but two. All women but one had significant worsening of proteinuria during pregnancy. One woman is currently on renal dialysis 2 years after the pregnancy, and three are expected to require it in the near future. All but one had hemoglobin A_1 levels <10 by delivery, and seven had normal levels. Two of the three group A women with preeclampsia were among this set. Unstable retinopathy complicated the course in three women with diabetic nephropathy. One required laser photocoagulation repeatedly during the second and third trimesters, and one needed vitrectomy. The third had florid background retinopathy that regressed after pregnancy and did not recur during a subsequent pregnancy.

Newborn morbidity. Infants of diabetic women in the study group were significantly less likely to be delivered before term than group B subjects (57% vs 74%, $p < 0.01$) but not to suffer morbidity (Table V). The requirements for intensive care, neonatal hypoglycemia, low Apgar score, and respiratory distress syndrome occurred with similar frequency in both the

Maximum serum creatinine	*Hypertension*	*$HgbA_1$**	*Comment*
1.2	Yes	10.3	Preeclampsia, healthy infant
1.8	No	7.0	Proliferative retinopathy, preeclampsia, premature labor, healthy infant
1.5	Yes	6.7	Proliferative retinopathy, normal newborn
0.8	No	9.2	Background retinopathy, normal newborn
0.7	No	9.6	Background retinopathy, premature labor, normal newborn
0.8	No	7.3	Background retinopathy, normal newborn
1.8	Yes	7.3	Normal newborn
1.0	No	7.2	Background retinopathy, normal newborn
3.0	No	5.4	Proliferative retinopathy, vitrectomy at 28 weeks, normal newborn
1.8	Yes	5.1	Proliferative retinopathy, fetal distress, healthy infant

study and control groups. The incidence of large (>4000 gm) or small (<2500 gm) infants did not differ. Only neonatal hyperbilirubinemia differed (11% vs 45%, group A vs group B, $p = < 0.01$). The nine infants suffering from respiratory distress syndrome (18% of the group) are detailed in Table VI. Five of these nine pregnancies were complicated by either premature labor or preeclampsia. The remaining four (8%) were at least potentially preventable. One mild case occurred despite amniotic fluid studies indicating maturity.

Neonatal morbidity is examined in relation to the degree of blood glucose control in Table VII. The incidence of both respiratory distress syndrome and early delivery, but not other newborn complications, is significantly less in women who achieved a delivery hemoglobin A_1 concentration of <8.5% (4% vs 27%, $p = < 0.05$; 38% vs 73%, $p = < 0.05$). The incidence of respiratory distress syndrome in infants was not related to the severity of diabetic complications in study group mothers. This complication occurred in two infants born of women with nephropathy and in seven infants of mothers in White classes B, C, and D (20% vs 17%, p = NS).

Fetal anomalies occurred with equal frequency in group A and B subjects (6% vs 10%, p = NS) (Table V). In the study group pregnancies complicated by fetal anomalies, two of the three occurred in women with extremely poor glucose control during embryogenesis (Table VIII).

Perinatal mortality. Two pregnancy failures occurred in both groups A and B (Table V). In group A both failures occurred in women who were poorly controlled (Table IX). One was caused by a fetal anomaly incompatible with life and intrauterine death. The other, which was preventable, occurred in a pregnancy complicated by failure of the mother to comply with medical advice. This woman refused both antepartum testing and hospitalization despite extensive counseling. Intrauterine death occurred at 35 weeks gestation. The perinatal mortality rate in study patients, including both, was 39/1000. Excluding the second patient, it was 20/1000. The rate in group B was 34/1000.

Comment

Outpatient management of type I diabetic gravidas improves maternal morbidity without compromising perinatal results. Hospitalization is a morbid complication of pregnancy. It contributes to emotional and financial hardship for the woman and her family and constitutes unnecessary expense. Only when necessary to produce medical benefits otherwise unattainable is it justifiable.

Although pregnancies in diabetic women have been managed successfully with minimal hospitalization,[4-6] extensive hospitalization is still practiced.[2,3] The intensive metabolic control efforts in our outpatient clinic were of the same degree as used in the hospital and were conducted under dietary and activity circumstances far more realistic than those found in the hos-

Table VI. Study group infants with respiratory distress

Patient No.	*White class*	*EGA*	*Hgb A_1*	*L/S*	*PG*	*Delivery*	*Comment*
1	C	33	11	–	–	C/S	Fetal distress in premature labor
2	C	36	11	–	–	C/S	Previous cesarean section, vulvar edema sufficient to cause skin necrosis
3	FR	32	10	–	–	C/S	Preeclampsia
4	C	28	12	–	–	C/S	Fetal distress
5	C	40	–	2.4	+	C/S	Labor induction
6	FR	33	7	–	–	C/S	Preeclampsia
7	C	31	12	–	–	C/S	Premature labor, breech
8	C	26	11	–	–	Vaginal	POL
9	B	38	10	–	–	Vaginal	Dysplastic kidney, spontaneous labor

EGA, Estimated gestational age; *Hgb*, hemoglobin; *L/S*, lecithin/sphingomyelin; *Pb*, phosphatidylglycerol; *C/S*, cesarean section; *POL*, premature onset of labor.

Table VII. Neonatal morbidity related to late pregnancy blood glucose control (hemoglobin A_1) in group A patients

	*Hgb A_1 <8.5% (N = 21)**		*Hgb A_1 >8.5% (N = 26)**			
	No.	*%*	*No.*	*%*	*p Value*	*95% confidence interval*
Respiratory distress†	1	4	7	27	<0.05	
Weight >4000 gm	5	24	5	19	NS	−0.36, 0.26
Required intensive care	3	14	7	27	NS	−0.14, 0.4
Hypoglycemia	6	6	6	23	NS	−0.05, 0.39
Hyperbilirubinemia	4	19	2	8	NS	−0.29, 0.07
Delivered at <38 wk	8	38	19	73	<0.05	

*Fourty-seven values are available, excluding two subjects with pregnancy loss and two in whom they were not obtained.
†In one infant with respiratory distress syndrome, hemoglobin A_1 was not available.

pital setting. When women were initially brought under control in the hospital, they commonly required reestablishment of control once discharged. Hospitalization of women decreased as the project progressed and was less than that used by others in attempting outpatient management of pregnant diabetic women.[4]

Group B women are not true controls, but rather a historic comparison group. Hospitalization periods for these women might have been influenced by their known greater incidence of preeclampsia (22% vs 6%). Nevertheless, it is true that hospitalization was used routinely during the years of their treatment, that this group was hospitalized far more, and that results with this method of treatment were not better than in those hospitalized less.

Hemoglobin A_1 level is a useful indicator of the establishment of glucose control over time. However, it is flawed because of the lag in this value in relation to decreases in blood glucose values. This 8-week lag is reflected in the number of study group women who failed to achieve acceptable levels by delivery. Many of these women had good control and significant decreases in hemoglobin A_1, but were admitted to the program too late to achieve normal levels by delivery. Except for this problem, hemoglobin A_1 levels offer a simple means to assess the control of study subjects.

The cesarean section rate in the study group was lower[7, 8, 12] or comparable with that in other studies.[2, 3] It was not different between the groups. The attempt made in group A women to allow spontaneous onset of labor or to defer induction until the cervix was favorable was directed at lowering the cesarean section rate, a goal not achieved. It may be true that improvement of metabolic control might allow continuation of pregnancies closer to the point of cervical ripening. Fetal well-being thus obtained could reduce the need for early induction of labor or cesarean section. No reduction in the cesarean section rate was observed in our well-controlled women, or in a very well-controlled group reported by Jovanovic and Jovanovic.[3] Most of the surgical deliveries in this group were indicated by fetal distress, maternal complications, large babies, and prior cesarean sections. The decrease in endometritis after delivery seen in group A women might reflect the more extensive use of prophylactic antibiotics during the years of this project.

Table VIII. Anomalies in 51 study group patients

Patient No.	*White class*	*Early pregnancy Hgb A_1*	*Comment*
1	B	14	Cardiac incompatible with life—stillborn
2	B	12	Dysplastic kidney—healthy infant
3	B	5	Dysplastic kidney—healthy infant

Hgb, Hemoglobin.

Table IX. Perinatal mortality in 51 study group patients

Patient	*White class*	*EGA**	*Initial Hgb A_1*	*Delivery Hgb A_1*	*Comment*
B.B.	C	35	16	12.9%	Refused antepartum fetal testing, refused admission, intrauterine deatrh
J.G.	C	31	14	11.1%	Atrophic left ventricle, aortic stenosis, heart block, intrauterine death

EGA, Estimated gestational age, *Hgb,* hemoglobin.
*At delivery.

The incidence of preeclampsia in group A women was not only much less than in the control group but was less than rates reported previously in diabetic women[2] and equal to our general population.[13] Although others have attempted to link this incidence to metabolic control[4] the relatively poor control in a number of group A women, at least by virtue of hemoglobin A_1 level, suggests no such association.

The women in group A with severe vasculopathy had no perinatal loses compared with two loses in each group. They were also under better metabolic control. The incidence of preeclampsia, a difficult diagnosis in women with significant proteinuria, was high in this group. The continuing morbid course of diabetic nephropathy in new mothers is well illustrated by the continuing severe renal insufficiency seen in four women. Given the opinion that diabetic vasculopathy is a risk factor for fetal anomaly,[14, 15] it is of interest that none of the three malformed infants were born to women in this group.

Newborn infants suffered no greater incidence of complications in the group treated as outpatients. They were delivered more frequently at term than their counterparts in the earlier group, although this conferred no apparent benefit in reduced morbidity, except in the reduction of neonatal hyperbilirubinemia. Respiratory distress syndrome occurred in 18% of group A infants, an incidence similar to that reported in diabetic women elsewhere.[2] This form of morbidity was far less in group A subjects who were well controlled (Table VII), and compared favorably with similarly well-controlled women.[2, 3] No such association was observed for neonatal hypoglycemia, which occurred for group A babies as a whole with a frequency comparable with that seen in well-controlled subjects.[2] Large and small infants complicated pregnancy results without respect to maternal glucose control, and newborn intensive care requirements were not dependent on control. These mixed results may relate to the degree of control accepted as good in this study. Furthermore, many women included in group A were not seen until relatively late in pregnancy, and the influence of both duration and degree of control might be reflected. As previously noted, the use of hemoglobin A_1 level as the index of control is simple and convenient, and third-trimester values correlate well with mean glucose determinations derived from individual glucose measurements over preceding weeks.[2] Therefore, it is an adequate assessment of duration and degree of control in the context of this report and effectively eliminates from the good control group women (Table VII) whose control was markedly improved only late in pregnancy.

Two perinatal deaths occurred in each group. Excluding one group A woman in whom the loss was not related to outpatient status but resulted from the refusal of care, the perinatal mortality rate was 20/1000, which is similar to that observed in both inpatient[2] and outpatient studies.[4]

The incidence of fetal anomalies was low in the 109 pregnancies. In group A women, two of three pregnancies resulting in malformed infants had poor control. In group B it was very good. Too few women in this study were controlled before pregnancy to have any realistic influence on anomaly rate.

The women and infants of group A might have ben-

efited from earlier and tighter control. They would not have benefited from more extensive hospitalization. The establishment of control is less efficiently done in the hospital, and even very frequent fetal monitoring can be managed in a clinic. Outpatient management of diabetic pregnant women suffers from no disadvantageous results not already a problem with women more frequently hospitalized. Fetal anomalies and morbidity, the principal consequences of diabetic pregnancy, are no more prevalent as a result of the setting in which the patient is managed.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. C. WILLIS SHERRER, Atlanta, Georgia (official guest). Dr. Bourgeois' paper is timely insomuch as it confirms what many of us have questioned for a long time: is it logical to place an individual in an artificial environment and formulate a treatment plan based on results of tests that likely will be invalid shortly after leaving this environment? We have often questioned the rationale, but as with so many other aspects of medicine, we are reluctant to change what is known, familiar, and comfortable.

The decade of the 1980s saw the development and refinement of home glucose monitoring, as well as continuous insulin infusion apparati. These innovations, combined with reliable techniques for the monitoring of fetal maturity and well-being, have made it immeasurably easier to manage and carry to maturity in many instances the insulin-dependent diabetic patient.

Dr. Bourgeois' paper is supportive of the overall movement in medicine toward outpatient management of situations that previously mandated hospitalization. For example, many operations are performed in outpatient settings that were previously considered an absolutely necessary inpatient procedure.

The author made the following points in his paper:

Maternal

A. The mean number of admissions was less in the study group and shorter than in group B.
B. Hospital stay at delivery was longer for group B.
C. Preeclampsia was less in group A.
D. Endometritis was less in group A.
E. Delivery routes were the same in both groups.

Newborn and fetal effects

A. The study group infants delivered later in pregnancy than group B.
B. The overall outcome in morbidity compared favorably in both groups.
C. Respiratory distress syndrome was lower in well-controlled pregnancies; however, overall the two groups were equal.
D. Fetal anomalies were the same in both groups.

Dr. Bourgeois makes the point that group B patients were for historical comparison only. I do not believe they are a true control group but were convenient.

There are a number of points to be derived from this study. First, the management is cost-effective. This is a finite amount of money available in the health care pool. If this pool is tapped too often and too deeply, resources will not be available in other needy cases. (At Piedmont Hospital in Atlanta, a 3-day stay to evaluate, educate, and institute treatment is about $1000.). Second, although no improvement in outcome was demonstrated in the study group, no harm was done either. Also, the close monitoring ("as often as daily" by telephone) compares favorably with inpatient care.

Although this is not the first paper to support outpatient management of pregnant diabetic patients, Dr.

Bourgeois' emphasis is unique in *total* outpatient management concept.

If these patients Dr. Bourgeois has studied in a university clinic situation can be motivated and educated to participate in their own care, imagine how much easier it would appear for us to take a group of private patients, who likely are better educated and motivated, through to a successful pregnancy outcome. Therefore this is a timely and supportive report and one from which all obstetricians should benefit.

Dr. Lawrence Devoe, Augusta, Georgia. I enjoyed this paper very much, and I think it supports a very important role of conscientious care in a very cost-effective setting. I have a few questions that came up during the presentation that I would like Dr. Bourgeois to address. The first is the use of hemoglobin A_{1c} as a method of monitoring glycemia. Most of us would agree that this method is of such long-term duration that it helps very little in understanding what our patients currently do at the time we see them. Second, how does chronic renal disease, such as that found in the nephropathy group, really affect the value of hemoglobin A_{1c}? Is the hemoglobin synthesis process affected by the nature of intrinsic renal disease?

The second question I have relates to the large number of patients in group A who had macrosomia. How often was this recognized before these patients were delivered and were these patients reviewed individually to confirm that their glycemic control met the standards of care that were established for this group?

Dr. Hugh Randall, Atlanta, Georgia. In this paper there was a push for outpatient management both in the private and public setting. I believe that if we try to look at cost containment, we will find that insurance companies will push just as hard and as far as they can without us trying to look for additional ways to do so. I am sure that there are many things that they pushed us into that are not particularly pleasing.

I believe that there are differences here, particularly in the incidence of marcosomia, toxemia, and endometritis and even subtle neonatal differences that may have been statistically significant and certainly would have been if the size of the study had been larger. Would you address what you calculated the power of the study would have had to be for those differences to be significant?

Dr. Bourgeois (Closing). I thank Dr. Sherrer for this thoughtful and considerate review. Regarding the use of hemoglobin A_{1c} as a monitor, as stated in the article, that is not really what we do. We monitor patients in day-to-day clinical settings according to blood glucose levels obtained by glucosemeters. Hemoglobin A_1 is primarily used in our clinic as an index because it is an attractive way to compare data. It is flawed but is simple, convenient, and avoids having to abstract large numbers of glucose determinations over long periods of time. In patient care it can be used as a cross-reference to glucose determinations that are done by the patients. I emphasize that we rely most heavily on the actual glucose determinations to assess ongoing control in a given patient.

Regarding the ability of chronic renal disease and bone marrow suppression to influence the values of hemoglobin A_{1c}, I would make two points. First, few of these patients had renal disease sufficient to cause bone marrow suppression in the first place. Second, since hemoglobin A_1 is expressed as a percentage of total, even if patients had anemia of chronic renal disease, hemoglobin A_1 levels would not be affected.

Regarding macrosomia, this may result more from less than ideal control and does not detract from the point that one can manage patients on the outside of the hospital as well as on the inside. As you are aware, the data supporting the notion that you can control macrosomia in diabetic patients simply by means of blood sugar control is mixed. I think that it is probably true that you can, but papers exist to support the notion that you cannot. Thus I believe the important point is that yes, some of these patients were less optimally controlled than we or you might desire them to be. That was not related to the outpatient setting but was related to the inability to control everybody as much as we want to.

We tried to lower our section rate compared with previous years but could not. However, our cesarean section rate in the worst of these patients was certainly no higher than is commonly reported even in well-controlled patients. I can cite one study of well-controlled diabetic patients managed preconceptually in which the cesarean section rate was still 50%.

Effectiveness of 1% lidocaine dorsal penile nerve block in infant circumcision

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A prospective, controlled, double-blinded investigation was conducted to evaluate whether infants undergoing circumcisions with 1% lidocaine dorsal penile nerve blocks experienced decreased stress as compared with those receiving saline solution injections or no injections. Stress was measured in terms of pulse rate and oxygen saturation on a pulse oximeter. A subjective grading scale was also developed to measure infant irritability. The total number in the study was 51 with 23 infants in the lidocaine group, 21 in the saline solution group, and 7 in the no injection group. The results of the study revealed an average increase of 28.8% in the pulse rate above baseline for the control infants ($p < 0.001$) versus no significant change in the lidocaine group. The average oxygen saturation of the control groups decreased by 5.6% from baseline ($p < 0.001$), and that of the lidocaine group decreased by 1.0%, which was not a significant change. The subjective data were gained by using a grading scale of 1 to 6 with 1 being the least irritable infant and 6 being the most irritable infant. The physician evaluation gave an average rating of 4.2 to the control group versus 2.4 for the lidocaine group ($p < 0.001$). The nursing evaluation during the procedure gave an average rating of 4.2 to the control group versus 2.3 to the anesthetized group ($p < 0.001$). The subjective evaluation of infants before and after the procedure was not significantly different. There were no major complications in any of the groups. (Am J Obstet Gynecol 1990;163:1074-80.)

Key words: Circumcision, anesthesia, lidocaine

Infant circumcision, despite the controversy that surrounds it, still remains one of the most common surgical procedures performed in the United States. The rate of circumcision in this country is reported to range from 70% to 90% in newborn male infants, and it does not appear to be declining.[1-4] The American Academy of Pediatrics recently reviewed its stand on infant circumcision, and it now states circumcision may have several medical indications including a reduction in the rate of urinary tract infections and the incidence of penile cancer.[7] Given this background, it appears that circumcision will be around for some time to come. In many areas of the country the obstetrician is still the primary physician involved both in helping the parent make an informed decision and in performing the procedure itself.

For generations this procedure has been safely performed without anesthesia or analgesia. In 1978 Kirya and Werthmann[5] introduced their technique of using lidocaine with a dorsal penile nerve block and showed it to be both safe and effective in reducing pain. Several studies have shown the effectiveness of the dorsal penile nerve block in reducing infant stress,[3-5] but the procedure has still failed to gain wide acceptance. This study was designed to assess the effectiveness of dorsal penile nerve block in reducing infant stress through the use of a pulse oximeter to measure infant responses in terms of oxygen saturation and pulse rate. A subjective grading scale was used to measure the amount of infant irritability observed by both the nursing staff and the physician performing the procedure.

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Material and methods

This study was approved by the Medical University of South Carolina Institutional Review Board for Human Research, and subjects were recruited into the study when the parents made a request to have their infant circumcised. Although no effort was made to encourage circumcision, all mothers were aware of its availability. Eighty-two percent of those who were asked to be in the study consented to participation and all signed an informed consent agreement.

Fifty-one infants from the low-risk newborn nursery at the Medical University of South Carolina participated in the study. Reasons for exclusion from the study included: gestational age < 36 weeks, weight < 2000 gm, brachial plexus injury, penile abnormality, Apgar score < 6 at 5 minutes, and suspected sepsis. The in-

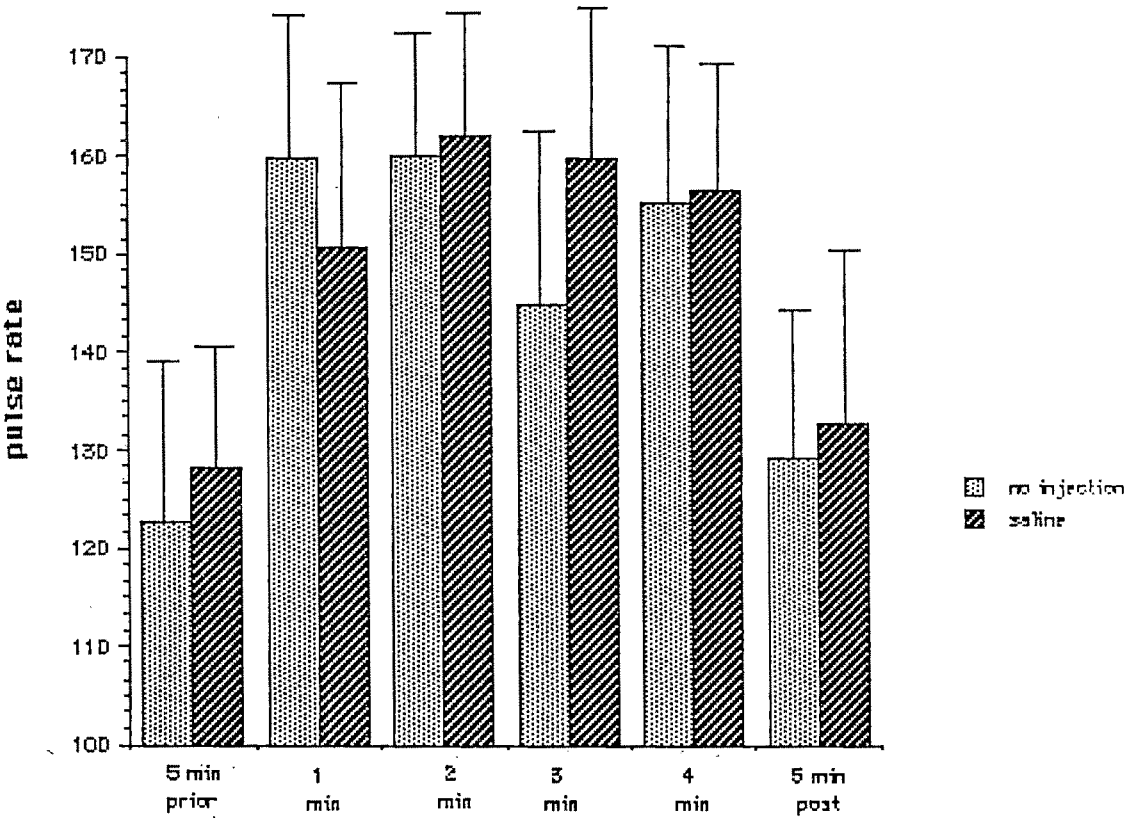


Fig. 1. Comparisons of pulse rate between saline solution group versus no injection group.

fants were divided by random selection through the use of cards into three groups. The first group (n = 23) received a 0.4 ml 1% lidocaine dorsal penile nerve block. The second group (n = 22) received 0.4 ml of normal saline solution in a similar fashion. The last group (n = 7) received no injections. The injections took place such that both the operator and the staff recording observations were blinded as to which infant was in which group. The average weight was 3208 ± 441 gm for the dorsal penile nerve block group versus the control groups 3304 ± 404 gm. The average gestational age of the dorsal penile nerve block group was 38.9 weeks versus 39.1 weeks in the controls. The average time since birth in the dorsal penile nerve block group was 26.0 hours versus 29.4 hours in the control groups. All infants were fasting for at least 90 minutes before the procedure, and they were monitored closely for aspiration throughout the procedure. The patients were placed on a standard circumcision board with extremities restrained. The pulse oximeter was attached to the right foot, and measurements were recorded as to the baseline heart rate and oxygen saturation in a noncrying state over 5 minutes. Measurements were taken at set 1-minute intervals during the procedure and at 5 minutes afterward.

All injection sites were prepped with alcohol, and injections were made in the manner described by Kirya and Werthmann[5] with placement at the base of the penis at the 10 and 2 o'clock positions and with a 26 gauge insulin syringe. The main difference in our technique and those described in previous studies was the use of 0.2 ml at each injection site as opposed to 0.4 ml. The injections were made in Buck's fascia approximately 2 to 3 mm from the skin surface with the physicians being careful to aspirate for blood before the injection. The penis was then prepped with povidone-iodine, and a standard Gomco Bell circumcision technique was used. Average circumcision time for both groups was 4.4 minutes. All infants were monitored for at least 2 hours afterward and urination was noted in all before discharge.

Initially, there were only two groups; one received a lidocaine injection and the other received saline solution. Some concern developed over whether injection of control saline solution could produce anesthesia, and a third arm was instituted in which a no injection control group was blinded by having the infant draped before the procedure. Seven patients were evaluated in this group, and comparisons with the saline solution group showed no significant changes in oxygen saturation or pulse rate between the two groups (see Figs. 1 and 2) with an unpaired Student t test. The results

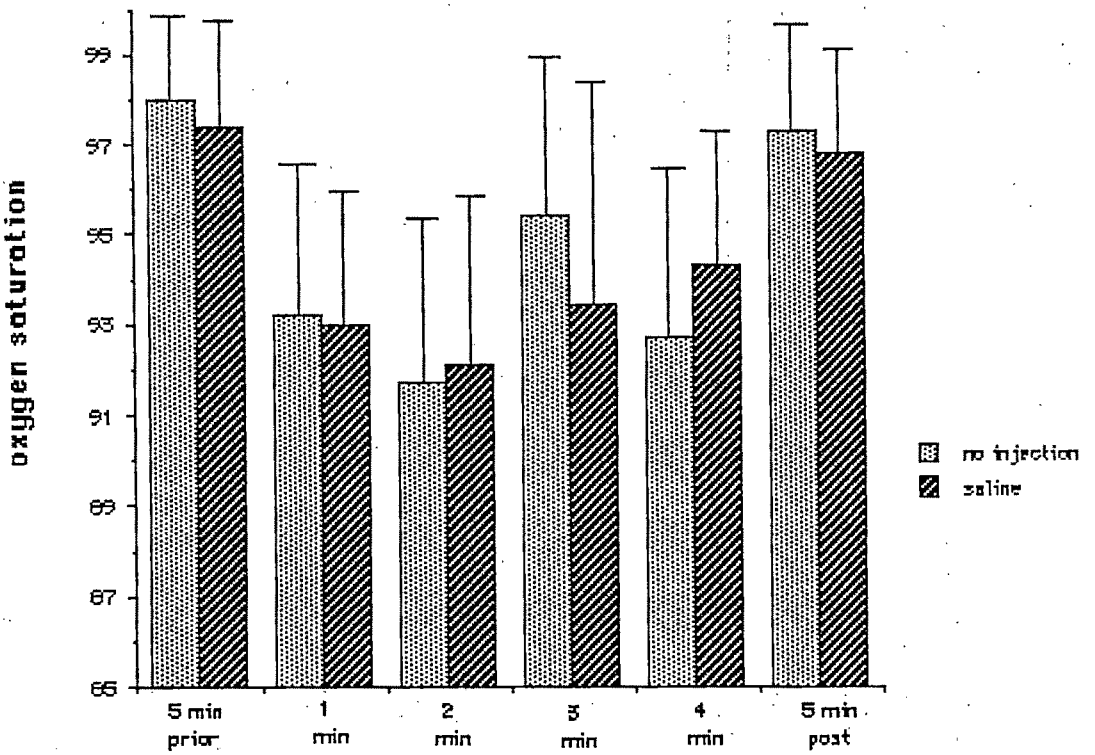


Fig. 2. Comparisons of oxygen saturation between saline solution group versus no injection group.

will show these two groups combined as one control group.

A subjective grading scale was developed and used by both the nursing staff observing the procedure and the surgeon performing the procedure. Infant irritability was graded on a scale of 1 to 6 with 1 representing the least crying or agitation and 6 the most. All nursing staff grading the procedure were experienced in newborn care and had observed multiple circumcisions. Ninety-one percent of the nursing evaluations were done by the same four senior members of the nursing staff. They were asked to grade the infant as to average irritability before the procedure, during the procedure, and 1 hour after the procedure. The surgeon was an obstetrics and gynecology resident experienced in circumcision, and he was asked to grade the infant's irritability during the procedure. He was also asked to assess whether he felt the infant was anesthetized. Eighty-five percent of the circumcisions were performed by the same senior resident. A second grading scale was used to assess bleeding from 1 to 3 with 1 being below average bleeding and 3 being above average. The surgeon was asked to use this scale during the procedure, and the nursing staff assessed the bleeding using this scale 1 hour after the procedure.

Results

Fig. 3 depicts the subjective grading results and shows that the physicians noted a significant difference in irritability during the procedure with the average being 4.2 ± 0.9 for the control group versus 2.4 ± 1.2 ($p < 0.001$ by unpaired Student t test). Physicians could correctly identify the anesthetized infant 81% of the time (17/21) and 100% of the infants that did not receive anesthesia were correctly identified. There was no significant difference in infant irritability noted between the groups by the nursing evaluation done before the procedure. Evaluation during the procedure showed an average of 4.2 ± 1.0 in the control group versus 2.3 ± 1.1 in the block group ($p < 0.001$ by unpaired Student t test). The postprocedure evaluation showed no statistical difference. The grading of both the bleeding during the procedure by the surgeon and the postprocedure evaluation by the nursing staff failed to show a statistical difference between the two groups. The control group was complicated by two episodes of postprocedural bleeding, one resolving with pressure and the other requiring suture. In the control group an infant also experienced one episode of emesis, which was easily resolved with suction. In the block group an infant experienced one episode of postprocedure bleeding, which stopped easily with pressure.

The pulse and oxygen saturation data were analyzed through the use of analysis of the variance with repeated measures between groups and over time. In this analysis any missing data points were estimated by using the group average at that evaluation time, thus giving an unbiased group error term. One member of each

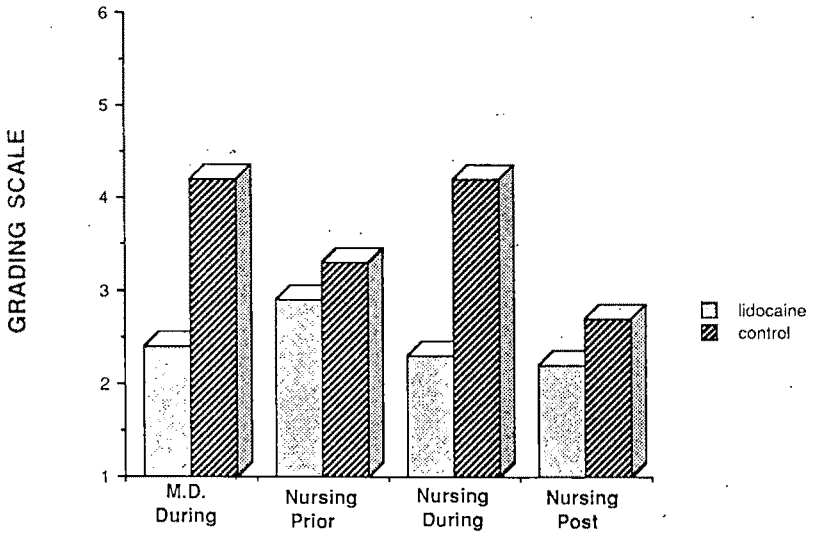


Fig. 3. Subjective grading of infant irritability.

group had multiple missing data points, and these were deleted from the analysis. The analysis documented a highly significant difference ($p < 0.001$) between the lidocaine and control groups in pulse rate and oxygen saturation. These differences were noted both between groups and over time.

Fig. 4 displays the comparison of the two groups' pulse rate during the study. The control group's average pulse rate rose 28.8% in a quadratic fashion from baseline, reaching a zenith at the 2-minute evaluation, and had returned to normal by the 5 minutes postprocedure evaluation. In the block group there was a very slight drop in the average pulse rate compared with baseline, this occurred in a skewed fashion. There was no significant difference found when the groups' baseline or 5 minutes postprocedure evaluations were compared.

Fig. 5 shows the comparison of oxygen saturation change in the two groups during the procedure. The control group showed a drop from a baseline average of 97.6 to a nadir of 92.2. The level then gradually rose to normal by the 5-minute postevaluation time; this occurred in a quadratic fashion. In contrast, the block group had a drop from 97.0 to a nadir of 96.0 with a gradual return to normal; this occurred in a skewed fashion. A comparison of the groups' baseline and 5-minute postprocedure evaluations showed no significant difference.

Comment

Circumcision has become part of United States social custom despite the controversy over whether there is truly an indication for its use. Given the recent change by the American Academy of Pediatrics on their stand against finding any indication for the procedure, I feel circumcision will continue being done at its present rate or even increase. Yet there seems to be little move to use penile nerve blocks, which have been proved through several studies to be safe and effective in the relief of the pain.[3-5]

This study has again demonstrated that lidocaine dorsal penile nerve block can effectively reduce the stress seen in infants undergoing circumcision. This study confirmed the data shown by Maxwell et al.[4] in 1987, that the oxygen saturation decrease typically seen with circumcision is significantly reduced through the use of a dorsal penile nerve block. Additionally, the rise in pulse rate typical in unanesthetized subjects also is prevented by penile nerve block. These changes have been documented in infants undergoing pain.[6, 8] The major difference in this study from the other data that have been previously presented is the use of less lidocaine to achieve the same response. We used 0.2 ml of lidocaine per injection site versus the 0.4 ml described by the other studies[3-5] and obtained similar findings.

Our subjective data also correlate with those found in studies by Stang et al.[3] and Kirya and Werthmann,[5] in that infants that undergo dorsal penile nerve blocks have less irritability during the procedure. The majority of the infants who have blocks will cry less and display less agitation than those without blocks. Physicians who performed the circumcision proved they could tell a difference in the infant's state by being correctly able to identify 81% of those infants anesthetized and 100% of those who were not, a finding previously reported by others.[4] This also points out that some blocks are unsuccessful and that some infants are going to be stressed from factors outside of the circumcision itself.

This study reiterates that this procedure is a simple, safe, and effective means of relieving the pain of circumcision. There have been a multitude of reasons given for why many physicians do not use this proce-

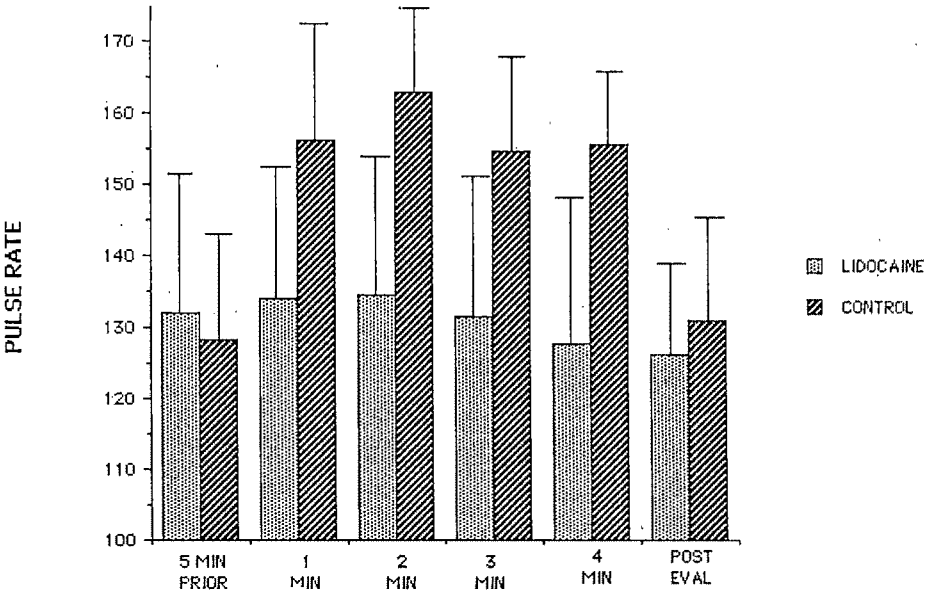


Fig. 4. Comparisons of pulse rate between control group versus lidocaine group.

dure, but surely we are building a large enough body of data to encourage its use and training throughout this country.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

Dr. Gene Burkett, Miami, Florida. Dr. Arnett and his colleagues have brought yet another study that endorses the efficacy of dorsal penile nerve block for circumcisions. Many other studies[1-3] in which dorsal penile nerve block was used for circumcision in newborns have shown reduction in pain, crying, agitation, and physiologic stress during the procedure. Prolonged agitation and reluctance to feed were minimal occurrences in dorsal penile nerve block circumcised newborns undergoing dorsal penile nerve block. On the other hand, if anesthesia was not used, heart rate rose by 34%, blood pressure by 15%, oxygen saturation decreased by 16%, and cortisol levels also were expectedly higher. With dorsal penile nerve block these side effects were markedly reduced statistically.

Despite this favorable situation, one survey[4] reported that only 23% of physicians used the technique of dorsal penile nerve block. Physicians who do not use the procedure are primarily under the guise: (1) that newborns do not feel intense pain during circumcision because of incomplete myelination of nerve pathways; (2) that immediate side effects are extremely shortlived, produce no long-lasting or residual deficits, and can be cushioned by tender loving care, (3) that dorsal penile nerve block itself adds pain and stress from the injection, together with the risks inherent in another step in the procedure.

Dr. Arnett and his colleagues are to be congratulated on this timely reminder that presents convincing data on the efficacy of dorsal penile nerve block in relieving intraoperative and postoperative irritability, pain, and tachycardia and in decreasing oxygen saturation. They report that when independent blinded observers (physicians and nurses) used grading scales of infant irritability, neonates with dorsal penile nerve block had significantly lower scores (less irritability) than the control group. Unfortunately the rating scale for irritability was omitted from the manuscript; had it been included,

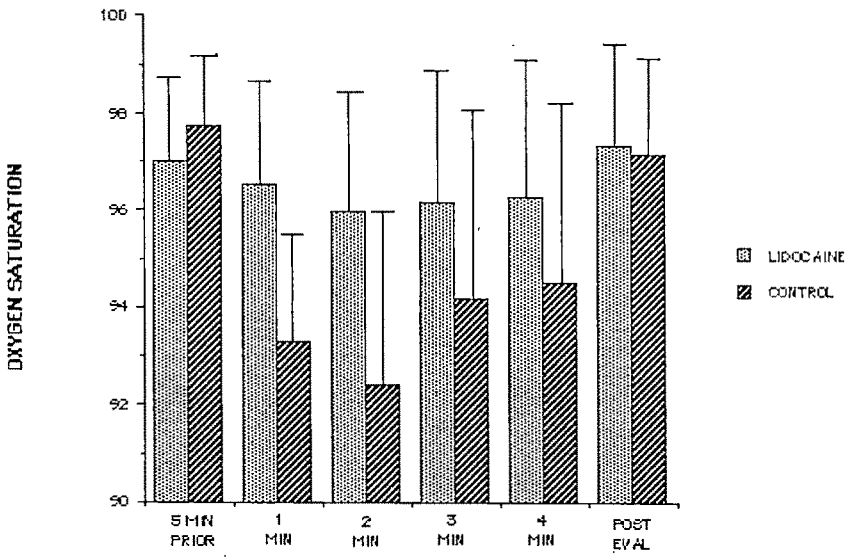


Fig. 5. Comparisons of oxygen saturation between control group versus lidocaine group.

it would have facilitated a more direct evaluation to the conclusions of the study.

Intraoperatively, oxygen saturation showed a greater decrease in the infants without block. A return to a normal level occurs by 5 minutes after operation. The authors did not explore the significance of this finding. At what time does the nadir occur and how long does it last? Are there any harmful effects produced by this change in oxygen saturation?

Perhaps, too, Dr. Arnett should have included data on irritability, pulse, and oxygen saturation *immediately* after injection and before circumcision. Since these authors recorded scores at 1-minute intervals, these data are available and their inclusion in the report would define the effect of the injection itself, a problem raised by nonusers of dorsal penile nerve block.

Another area of concern is the study groups. Initially, Dr. Arnett and colleagues started with two groups—one received lidocaine and the other saline solution injections. When concern "over whether control saline could produce anesthesia" arose, the investigators subdivided the saline control group and reported on seven neonates in whom no injection was used. This changed the study design, as well as the control group, and weakened the statistical power[5] of the conclusions. From this perspective no valid conclusions can be made, especially on the noninjected neonates. A larger number of noninjected neonates should be studied separately as a third group in the original concept.

The differences between the lidocaine group and the remaining saline solution group, 23 in total, are, however, sufficient enough to indicate trends strong enough to support the efficacy of the dorsal penile nerve block.

Even using 0.2 ml of lidocaine at each site, half of the dose recommended in other studies, Dr. Arnett and associates have shown us a simple, easy, effective method of controlling pain and irritability without increasing the overall complication rate of circumcisions, reportedly 0.2% to 0.6%. Perhaps the real question to be put is not whether we should be routinely using dorsal penile nerve block but rather whether proper genital hygiene would effectively reduce urinary infections in the uncircumcised infant. The American Academy of Pediatrics[6] in its concern for an increased incidence of urinary tract infections among uncircumcised infants, emphasized that mothers of newborns should be advised of this recent finding as an important part of the decision-making process for circumcision. Notwithstanding this new position, the message from Dr. Arnett and colleagues is that the procedure can be performed safely and humanely. The crying, agitated newborn is indeed in pain, with dorsal penile nerve block, there is no longer an excuse not to relieve that agony. We thank them for that rejoinder.

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Dr. David Soper, Richmond, Virginia. Did you consider using infants who were not circumcised at all as a control group? Second, subjective scales by their nature cannot really be considered continuous data. Probably a more appropriate statistical test would be the Mann-Whitney V test.

Dr. Frank Greiss, Mooresville, North Carolina. Dr. Arnett, I think Dr. Burkett asked this question, but I will ask it again. Did you actually look at the parameters before and while you were doing the nerve block itself? Would you describe for me who trained your residents to do circumcisions at the Medical University of South Carolina, and what sort of a formal process do you go through to do this?

Dr. John W. C. Johnson, Gainesville, Florida. I want to congratulate you, Dr. Arnett, on a nice study. It was one that needed to be done. I was very curious about the drop in oxygen saturation. Do you have an explanation for that?

Dr. Arnett (Closing). The grading scale is something that was added on. I was actually just going to measure pulse rate and oxygen saturation, and then I thought a scale would not be a bad thing to look at. We really did not put as much attention into our scale as we should have, and I am not sure what that data really mean. They definitely show that people could tell a difference even with a very widely subjective scale.

We did have some data right after the injections took place. Looking at what happened to oxygen saturation and crying, on average, they resolved in 30 seconds after the injection. Obviously some infants cried more than others, but on an average the pulse returned to normal and the oxygen saturation returned to normal very quickly. We did determine these on the first 35 patients that we had in the study, but I did not present those data.

Regarding Dr. Greiss' question on how we were trained, our residents in the first-year level are generally taught by the senior residents. Our first-year residents go in with the senior residents and learn to do circumcisions under their guidance. When we feel they are performing them on a level that we can leave them alone, we do. This generally is in the first few months. We are not teaching the block to residents as a manner of routine, but I encourage them to use it and teach my technique when requested.

Finally, regarding the drop in oxygen saturation, there have been several studies by anesthesiologists showing any infant under stress can undergo a drop in oxygen saturation. I am sure that this is what is happening when the baby cries or is under a certain amount of stress; the oxygen saturation typically drops a certain degree.

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Reducing cesarean sections at a teaching hospital

Luis Sanchez-Ramos, MD,[a] Andrew M. Kaunitz, MD,[a] Herbert B. Peterson, MD,[b] Beverly Martinez-Schnell, PhD,[b] and Robert J. Thompson, MD[a]

Jacksonville, Florida, and Atlanta, Georgia

A department-wide effort to reduce the cesarean section rate at the University Medical Center of Jacksonville (Florida) began in 1987. University Medical Center, a teaching hospital with approximately 4500 annual deliveries, serves an almost exclusively indigent obstetric population. Overall, the cesarean section rate declined from 28 per 100 deliveries in 1986 to 11 per 100 in 1989. Decreasing the number of repeat cesarean sections played an important role in reducing total cesarean deliveries. In 1986 32% of women with prior cesarean sections underwent a trial of labor. By 1989 this proportion had increased to 84%. In 1986 65% of women undergoing a trial of labor were delivered vaginally. By 1989 this proportion had increased to 83%. For these reasons the proportion of patients who had repeat cesarean sections dropped from 8% in 1986 to 3% in 1989. Changing approaches to the evaluation and management of dystocia and fetal distress also helped to lower the overall cesarean section rate. In 1986 cesarean sections for at least one of these two indications accounted for 14% of all deliveries. By 1989 this percentage had dropped to 4%. Because selective criteria for vaginal delivery of fetuses in breech presentation were maintained, incremental increased rates of vaginal breech delivery had only a minimal impact on lower overall cesarean section rates. The reduction in the number of cesarean sections was accomplished without compromising neonatal outcomes. In fact, during this 4-year period neonatal mortality rates actually decreased; neonatal morbidity rates remained stable. Our experience suggests that cesarean section rates can be substantially reduced without compromising the newborn. (Am J Obstet Gynecol 1990;163:1081-8.)

Key words: Cesarean section, perinatal outcome, trial of labor

In the United States the rate of cesarean sections has quintupled from 5% of obstetric deliveries in 1964 to greater than 25% in 1988.[1] Some have suggested that this increase in cesarean deliveries has played a major role in lowering neonatal mortality.[2] Others note the negative impact high cesarean rates have on maternal health[3, 4] and obstetric care costs.[5] Although a broad consensus agrees that current rates of cesarean section are excessive, the number of such deliveries remains high. This article describes efforts to reduce cesarean sections at a teaching hospital.

Material and methods

University Medical Center of Jacksonville, one of 10 regional perinatal centers in Florida, serves a largely high-risk, low-income obstetric population. All obstetric patients are cared for by resident physicians in obstetrics and gynecology and nurse-midwives supervised by full time faculty members.

Beginning on July 1, 1987, a recently hired faculty perinatologist (L.S.R.) introduced new guidelines regarding intrapartum management of women with prior cesarean sections. Patients with one or two previous cesarean sections were counseled regarding the benefits of trial of labor. Patients with low transverse and vertical scars not extending into the uterine corpus were considered candidates for trial of labor. Patients with either a previous classic cesarean section, myomectomy in which the uterine cavity had been entered, or previous uterine incisions of unknown type were not considered candidates for vaginal delivery. The option of electing a repeat cesarean section was not routinely offered to patients who otherwise were appropriate candidates for trial of labor. Patients with prior cesarean section(s) who requested postpartum sterilization likewise were not routinely offered a cesarean section.

The intrapartum management of the patients undergoing a trial of labor included continuous electronic fetal monitoring. After rupture of membranes an intrauterine pressure catheter and fetal scalp electrode were applied. As for other intrapartum patients, oxy-

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Table I. Cesarean sections among total deliveries at University Medical Center, Jacksonville, 1986 to 1989

	1986 (N = 4350)		*1987 (N = 4285)*		*1988 (N = 4493)*		*1989 (N = 5163)*		*Difference, 1989-1986*	
Cesarean sections	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*%*	*p Value*
Primary	849	19.5	643	15.0	424	9.4	374	7.2	−12.3	$p < 0.0001$
Repeat	349	8.0	319	7.4	174	3.9	168	3.3	−4.7	$p < 0.0001$
TOTAL	1198	27.5	952	22.4	598	13.3	542	10.5	−17.0	$p < 0.0001$

tocin for induction and augmentation or both and epidural anesthesia were used.

New guidelines for performing primary cesarean section were also established in July, 1987; these considered dystocia, fetal distress, and fetal malposition as potential indications. Dystocia was diagnosed according to the criteria outlined by Friedman.[6] Cesarean delivery for arrested dilatation was performed after no further dilatation was noted with more than 2 hours of regular uterine contractions (≥150 Montevideo units), whether contractions occurred spontaneously or as a result of oxytocin augmentation. Other diagnoses classified as arrest disorders were prolonged deceleration phase (>3 hours for nulliparous women and ≥1 hour for multiparous patients), and arrest of descent (no progression in descent for more than 1 hour for nulliparous women or for more than 30 minutes for multiparous women) during the second stage of labor.[7] In cases of arrest of dilatation as a result of a hypocontractile pattern, cesarean section was performed only if at least 4 hours of contractions achieved with oxytocin failed to progress labor. Medically indicated induction of labor in patients with unfavorable cervices was preceded by cervical ripening with either prostaglandin gel (4 mg of Prostin E_2, The Upjohn Co., Kalamazoo, in 6 ml of sterile lubricant) or Hypan (Dilapan, Gynotech Inc., Lebanon, N.J.) osmotic dilators.[8, 9]

Fetal distress suggested by electronic fetal monitoring was confirmed by scalp pH sampling. When the extent of cervical dilatation did not permit scalp sampling, fetal acoustic stimulation was performed.[10] A rise of 15 beats/min above the fetal heart rate baseline for a duration of at least 15 seconds was considered reassuring.

Vaginal delivery of breech fetuses was performed only if the following criteria were met: (1) frank or complete breech presentation; (2) adequate x-ray pelvimetry without hyperextension of the fetal head; (3) ultrasonographically estimated fetal weight between 2500 and 4000 gm; and (4) presence of an obstetrician with experience in breech deliveries. For patients with singleton gestations between 36 and 39 weeks in which the breech presentation was identified antepartum, external cephalic version was attempted. Twin pregnancies with a nonvertex second twin were managed according to the criteria of Chervenak et al.[11] After the birth of the first twin, external cephalic version was attempted if the second twin was not vertex. If the version was not successful and the estimated fetal weight was ≥2000 gm, a cesarean section was performed after failed version.

At weekly conferences, departmental resident and obstetric faculty physicians reviewed each cesarean section and focused on indications for abdominal delivery. Particular attention was paid to electronic fetal monitoring records, umbilical cord gas results, and Apgar scores. In autumn of 1989 a sustained decline in the overall cesarean section rate was noted by the faculty at University Medical Center. For this reason it was decided to scrutinize neonatal morbidity and mortality while continuing to monitor cesarean section trends. This article documents the impact of changing clinical intrapartum management policies.

We computed annual proportions of primary and repeat cesarean sections from 1986 to 1989. For each year, primary sections were classified by indication. We tested the difference between the proportions in 1986 and 1989 for statistical significance.[12] Similar tests for difference were performed for the proportion of trial of labor among women with prior cesarean section, the proportion of vaginal birth among women undergoing a trial of labor, the neonatal and perinatal mortality rates, and adverse neonatal outcome rates. During the same years (1986 to 1989), cesarean section rates, neonatal intensive care unit admission rates, and neonatal mortality rates were tested for difference in each of five birth weight categories.

Results

Cesarean sections. The overall cesarean rate decreased steadily from 27.5% of deliveries in 1986 to 10.5% in 1989 ($p < 0.0001$) (Table I). Decreased rates of cesarean section occurred among women who had infants in all birth weight categories; these decreases were statistically significant for all categories except for women who had infants weighing >4500 gm (Fig. 1). The rates of primary cesarean sections fell from 19.5%

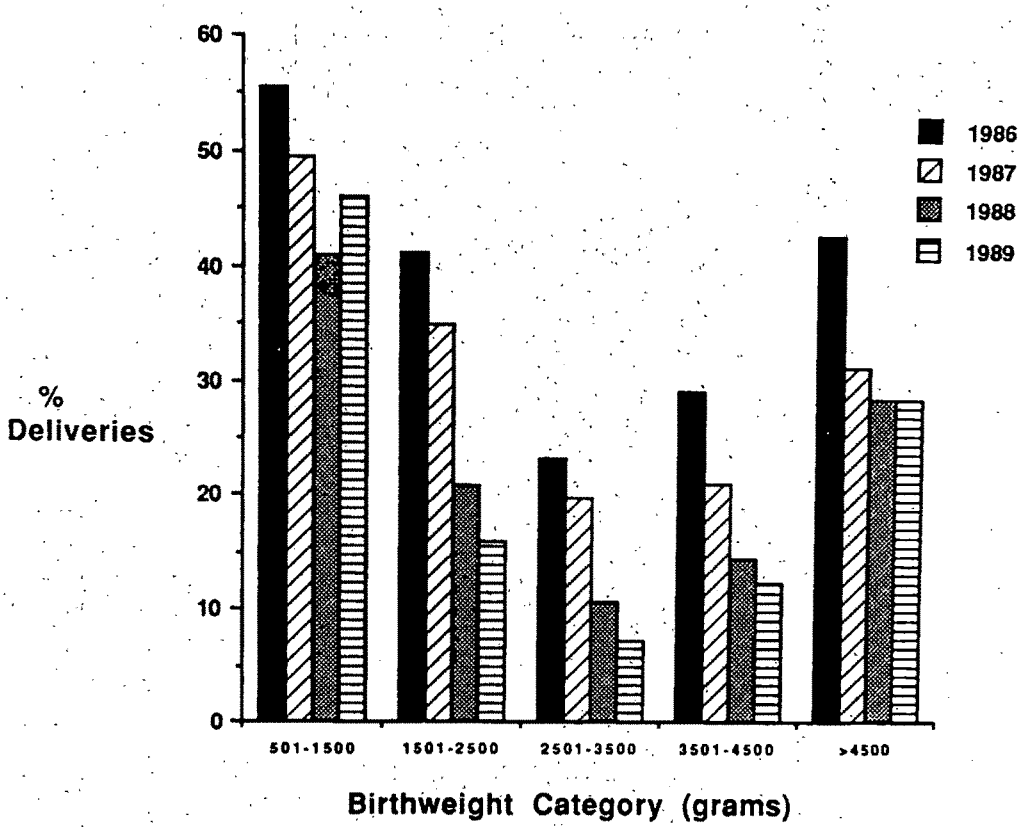


Fig. 1. Birth-weight-specific cesarean section rates, 1986 to 1989.

Table II. Deliveries of women with prior cesarean section, University Medical Center, Jacksonville, 1986 to 1989

	1986		*1987*		*1988*		*1989*		*Difference (1989-1986)*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*%*	*p Value*
TOL	139	31.7	193	41.9	381	76.5	487	83.9	52.2	$p < 0.0001$
Proportion of women undergoing TOL with subsequent vaginal birth	90	64.7	142	73.6	342	85.0	403	82.7	18.0	$p < 0.0001$
Proportion of all women delivered after prior cesarean with subsequent vaginal birth	90	20.5	142	30.8	342	65.1	403	69.4	48.9	$p < 0.0001$

TOL, Trial of labor among women with prior cesarean sections.

to 7.2% ($p < 0.0001$), whereas repeat cesarean sections declined from 8.0% to 3.3% ($p < 0.0001$). While rates of cesarean sections decreased, operative vaginal deliveries (forceps and vacuum) remained stable (16.2% of all vaginal deliveries in 1986 versus 18.5% in 1989).

Decreased repeat cesarean sections played a key role in the overall reduction in cesarean deliveries. From 1986 to 1989 the proportion of patients with prior cesarean deliveries who underwent a trial of labor increased from 32% to 84% ($p < 0.0001$). During these same years the proportion of women undergoing a trial of labor who had subsequent vaginal births increased from 65% to 83% ($p < 0.0001$). Among all women who were delivered after a previous cesarean section, the percentage who had a subsequent vaginal birth increased from 20.5% to 69.4% ($p < 0.0001$) (Table II).

Decreased rates of cesarean section for dystocia and fetal distress also contributed to overall reduction in cesarean delivery. From 1986 to 1989 rates of primary cesarean section for dystocia declined from 7.2% to 2.9% ($p < 0.0001$) and for fetal distress from 6.7% to 1.5% ($p < 0.0001$) of all deliveries (Table III). Cesarean

Table III. Primary indications for cesarean sections among total deliveries, University Medical Center, Jacksonville, 1986 to 1989

Indication	1986 (N = 4350)		1987 (N = 4285)		1988 (N = 4493)		1989 (N = 5163)		Difference, 1989-1986	
	No.	%	No.	%	No.	%	No.	%	%	p Value
Dystocia	313	7.2	233	5.4	140	3.1	150	2.9	−4.3	$p < 0.0001$
Fetal distress	291	6.7	225	5.3	110	2.4	79	1.5	−5.2	$p < 0.0001$
Malpresentation	130	3.0	108	2.5	108	2.4	106	2.1	−0.9	$p < 0.01$
Other	115	2.6	77	1.8	66	1.5	39	0.8	−1.8	$p < 0.0001$
Total primary cesarean sections	849	19.5	643	15.0	424	9.4	374	7.2	−12.3	

Table IV. Perinatal and neonatal mortality, University Medical Center, Jacksonville, 1986 to 1989

	1986	1987	1988	1989	Difference, 1989-1986	
					%	p Value
Neonatal deaths	71	41	35	33		
Fetal deaths	67	43	43	44		
Live births (denominator)	4336	4270	4470	5157		
Neonatal mortality rate*	16.4	9.6	7.8	6.4	−10.0	$p < 0.001$
Perinatal mortality rate†	31.8	19.7	17.4	14.9	−17.4	$p < 0.0001$

*Based on deaths occurring at <28 days of life per 1000 live births.
†Fetal deaths plus neonatal deaths per 1000 births.

section for breech and other fetal malpresentations decreased from 3.0% to 2.1% of deliveries during the years 1986 through 1989, which represented a small but statistically significant change.

Perinatal outcome. Overall, the perinatal mortality rate decreased from 31.8 in 1986 to 14.9 in 1989 ($p < 0.0001$), whereas the neonatal mortality rate decreased from 16.4 to 6.4 ($p < 0.0001$) (Table IV). Birthweight-specific neonatal mortality declined in infants weighing <2500 gm, and rates remained stable in higher-birth-weight categories (Fig. 2). Because the number of neonatal deaths in each category was small, the decrease was not statistically significant.

The incidence of low 1- and 5-minute Apgar scores and neonatal seizures remained stable over the 3-year study period. During these years no consistent trends were observed in either incidence of neonatal intensive care unit admissions or length of neonatal intensive care unit stay. In 1989 there was a statistically significant reduction in the proportion of newborns admitted to the neonatal intensive care unit (Table V, Fig. 3).

Comment

Elimination of elective repeat cesareans, active management of dystocia, and an approach to suspected fetal distress that emphasized intrapartum confirmation contributed to the reduction of overall cesarean sections at University Medical Center from 1986 to 1989. Of all women who were delivered after a previous cesarean section, 69% had subsequent vaginal births in 1989; the comparable U.S. national estimate for 1987 was 9.8%.[13]

Our approach to trial of labor after prior cesarean is based on two assumptions. First, trial of labor after one or two prior cesarean sections in which uterine incision(s) involved only the lower segment is safe.[14, 15] Second, higher morbidity and health care costs[1] of elective repeat cesarean section outweigh the advantages that individual patients or their obstetricians may perceive.

Active management of dystocia, as described earlier in this report, also played an important role in reducing the number of cesarean sections at our institution. Similar intrapartum protocols have resulted in lower rates of cesarean section for dystocia in other institutions. Myers and Gleicher[16] were able to reduce their cesarean section rate from 17.5% to 11.5%. Porreco[17] demonstrated that a low cesarean section rate (6%) can be achieved without compromising neonatal outcome. Similarly, reports from Ireland[18] have consistently documented a very low cesarean section rate (4% to 6%) without undue perinatal morbidity or mortality.

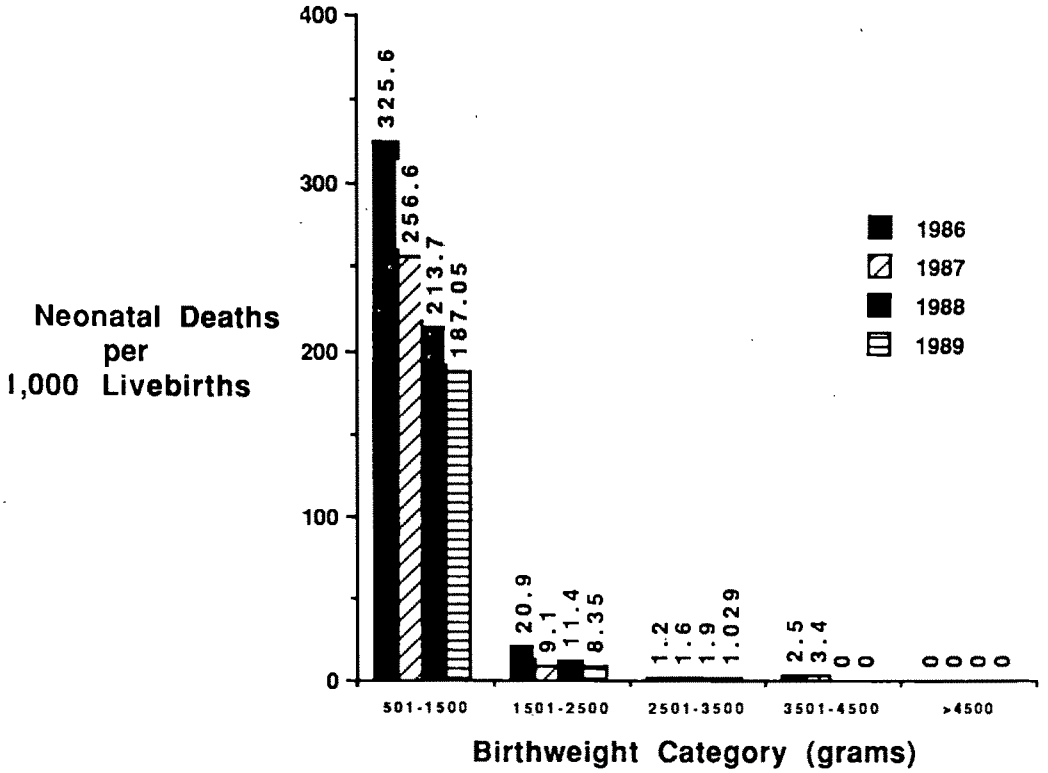


Fig. 2. Birth-weight-specific neonatal mortality rates, 1986 to 1989.

Table V. Adverse neonatal outcomes among total live births, University Medical Center, Jacksonville, 1986 to 1989

	1986 (N = 4336)		*1987 (N = 4270)*		*1988 (N = 4470)*		*1989 (N = 5157)*		*Difference, 1989-1986*	
Outcome	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*%*	*p Value*
Apgar score < 7										
1 min	457	10.5	357	8.4	476	10.6	571	11.0	+0.5	$p > 0.40$
5 min	79	1.8	65	1.5	83	1.9	90	1.7	−0.1	$p > 0.80$
NICU admission	447	10.3	420	9.8	432	9.7	453	8.8	−1.5	$p < 0.05$
NICU LOS (days)										
Mean	19		15		15		16			
Mode	2		3		3		3			
Median	6		4		5		5			
Neonatal seizures	108	2.5	120	2.8	116	2.6	114	2.2	−0.3	$p > 0.40$

NICU, Neonatal intensive care unit; *LOS,* length of stay.

Our approach to cesarean section for fetal distress emphasized fetal scalp pH testing when feasible to improve the precision of this diagnosis. This strategy acknowledges the low positive predictive value of electronic fetal monitoring as a sole indicator of fetal distress.[19]

Because selective criteria for vaginal delivery of fetuses in breech presentation were maintained, incremental increased rates of vaginal breech delivery had only a minimal impact on lowering overall cesarean section rates at University Medical Center. In a report of another program to lower the number of cesarean sections, a liberalized approach to vaginal breech delivery was associated with three neonatal deaths among breech presentation fetuses.[16] Some authorities have criticized this liberalized approach to vaginal breech delivery.[20, 21] We support maintenance of selective criteria for vaginal delivery of breech presentation fetuses,

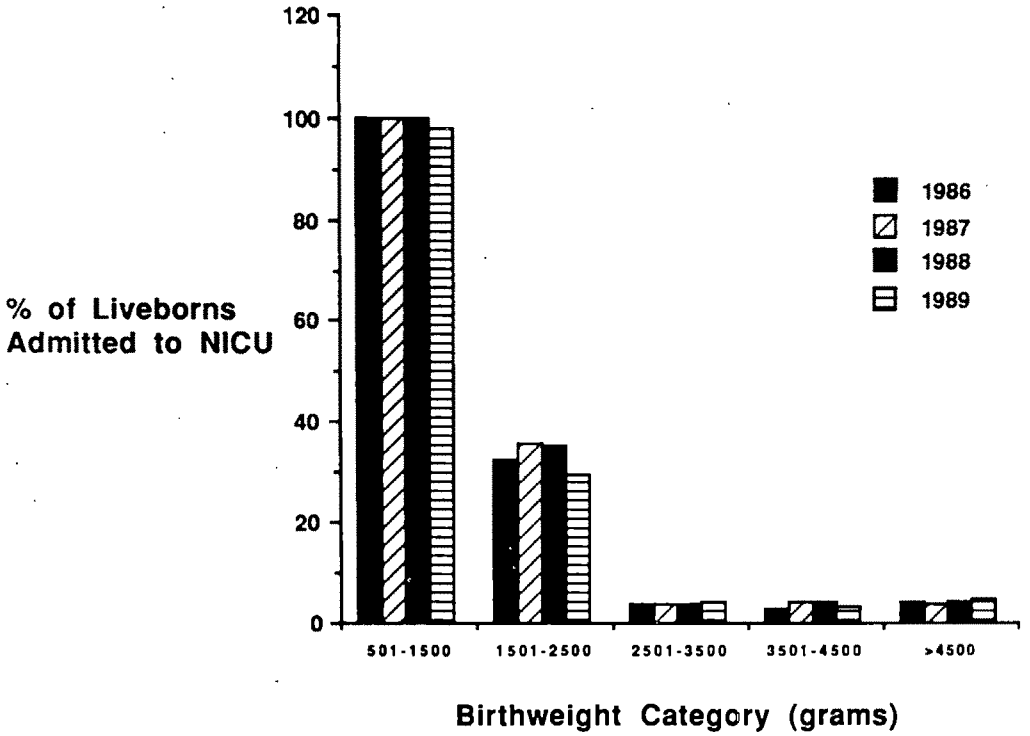


Fig. 3. Birth-weight-specific neonatal intensive care unit admissions, 1986 to 1989.

and also underscore that the number of cesarean sections can be substantially reduced without major alterations in managing obstetric malpresentations.

Our finding that perinatal and neonatal mortality rates decreased concurrently as the number of deliveries decreased should not be overinterpreted. These declines in mortality rates could well be attributable to factors other than method of delivery. Data from the National Infant Surveillance project (unpublished) found higher mortality rates for those infants weighing ≥1000 gm delivered by cesarean section. Although we believe our data strongly suggest that reductions in cesarean section can be accomplished without increasing risk to infants, only a randomized clinical trial could test that hypothesis.

Our success in lowering cesarean section rates is largely attributable to our centralized approach to intrapartum decision making. Although others have used such a centralized approach successfully,[18] it contrasts with other approaches many obstetric units in this country use, in which cesarean section rates for individual obstetricians may vary markedly. Goyert et al.[22] noted that rates of cesarean delivery for different physicians at a community hospital serving an affluent population ranged from 19% to 42%. Their analysis suggested that the individual clinician's practice style itself was a major determinant of the wide variations in rates of cesarean section. Implementing standardized protocols regarding repeat cesarean sections, dystocia, and fetal distress requires substantial commitment and effort from obstetricians and others who care for obstetric patients. However, our experience suggests that such an effort can substantially reduce rates of cesarean delivery without compromising the newborn.

Addendum

During the first 6 months of 1990, the overall cesarean section rate has continued to decrease (8.6%), without an evident increase in perinatal morbidity and mortality.

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR. ROBERT G. BRAME, Greensboro, North Carolina. This article covers an obviously timely topic. Despite much that has already been written, the continuing appropriateness of the topic results from the great disparity that persists in actual practice compared with a now abundant literature that suggests that the cesarean section rate is too high. This report documents the achievement of a very low cesarean section rate in an indigent and high-risk population, with a reduction in the combined section rate from 27% in 1986 to 11% in 1989, with an attendant reduction in perinatal and neonatal mortality rates; this is principal point of the article. The authors demonstrate quite clearly that a dedicated (and if I may read between the lines) intense effort to reduce the cesarean section rate can be successful. By the standard measures we use perinatal morbidity seems to certainly be no worse, but this is obviously a much more difficult assessment to make. I commend the authors for this excellent work but I do have some questions.

Although you emphasize that elimination of elective "repeat cesarean sections played a key role in the overall reduction in cesarean deliveries," I note that, according to Table I, the reduction in primary cesarean section almost exactly duplicated the reduction in repeat sections; I am a bit puzzled by this emphasis. Since you do not give patients with previous cesarean sections the option of a repeat cesarean delivery, I would like to know what you tell them. Do you have patients who demand a repeat cesarean section, and what do you do with them? I suspect my patients are similar to yours, and I have some patients for whom no amount of education or paternalism will convince the patient that she should be delivered vaginally. In addition, I have problems dealing with unfavorable and unengaged postdate pregnancies, labor in patients with previous section with unengaged fetal parts, and excessively large fetuses that are unengaged; these situations balloon my cesarean section rates. I wonder if you have ways of dealing with these circumstances that might help us.

Finally, although the last word on this topic has obviously not been written, cesarean section rates *can* be reduced, but to what degree this is really in the best interest of patients is not quite so clear. I spent most of my adult life adjusting to a belief that cesarean section was all right, and now I am trying to adjust to your implied suggestion that I may be performing too many cesarean sections. I do not know what the section rate ought to be. I do know, as a practitioner, that the decision to perform or not perform a section, particularly in a private, well-educated population, is rarely a simple matter of strict medical indication. In conclusion, we obviously can reduce the cesarean section rate, and the best scientific information suggests we can do that safely and that we ought to try. This presentation is an excellent documentation that a reduction can be achieved and I congratulate the authors on this effort. Yet to be answered, however, is the question encompassing all of those other considerations that enter into a decision: our legal climate, patient autonomy versus medical paternalism, and desire by patients and doctors to control events and their timing by surgical delivery.

DR. WILLIAM KIRKLEY, Fort Lauderdale, Florida. I have several questions. Did you have any patients with ruptured uteri? I presume you did not since you did not mention it. Second, when I was practicing obstetrics and the fetal heart monitor strip would be slightly abnormal or moderately abnormal, I would rush to do a cesarean section. I am sure you have had similar cases in your hospital. Do you rely solely on the fetal scalp pH? Third, do you have any potential lawsuits regarding these cases? If you have a monitoring problem during labor, you will be sued if you do not take action immediately.

DR. WILLIAM S. GRIZZARD, JR., Petersburg, Virginia. Do you allow patients with either twin pregnancy or breech presentation to undergo a trial of labor?

DR. HUGH RANDALL, Atlanta, Georgia. This article suggests the need for an individual, if not a committee, within the hospital to scrutinize cesarean sections. I know that in our community cesarean section rates around 35% are common. When there are individuals

like Dr. Sanchez-Ramos to study these services and to perform the type of peer review that was done at this institution, I think we will really be able to reduce the cesarean section rate. In many cases his review perhaps made him an unpopular individual. I would ask Dr. Sanchez-Ramos how many times he or his committee had to point out to a physician that he had not met the criteria for doing the cesarean section, for example, for dystocia?

DR. SAMIR BEYDOUN, Miami, Florida. You emphasized that there is no increase in the neonatal morbidity and mortality. I would like to ask Dr. Sanchez-Ramos to compare the maternal morbidity in cases with failed trials of labor that ultimately needed a repeat cesarean section and those with elective repeat cesarean section.

DR. GENE BURKETT, Miami, Florida. In Miami we have a large migrant population. How do you handle cases with unknown scars?

DR. SANCHEZ-RAMOS (Closing). First, I will address Dr. Brame's concern about not giving our patients a choice between repeat cesarean sections and a trial of labor. In accord with recommendations of the American College of Obstetricians and Gynecologists, we do not routinely perform elective repeat cesarean sections. We believe that vaginal birth after cesarean section is a much safer procedure than a repeat cesarean section. There are currently no reports in the literature of maternal deaths directly attributable to vaginal births after cesarean sections. In contrast, maternal deaths as a result of repeat cesarean sections do occur.

Dr. Kirkley had a question regarding ruptured uteri. I am not aware of a true ruptured uterus occurring in a patient with a previous cesarean section undergoing a trial of labor. Occasionally we have noted "windows" or dehiscences. The most serious dehiscence that I recall was in a patient with a previous low vertical scar who was undergoing an elective repeat cesarean.

With regard to the use of scalp pH sampling and electronic fetal monitoring, we use the former to complement the latter. Rather than rely solely on scalp pH results or alterations in the fetal monitoring tracing, we use both modalities together.

I am unaware of any lawsuits directly related to our management protocol for cesarean sections.

With regard to management of twins we currently allow patients with twins and previous cesarean sections a trial of labor.

Peer review has been one of the most important factors contributing to the reduction of cesarean sections at our hospital. All our practicing obstetricans are full-time faculty members. We do not have private practitioners. All the cases discussed at our cesarean section review meetings are those performed by the residents under faculty supervision; critiquing of individual cases is therefore facilitated. I may occasionally become unpopular if a resident feels he or she is not performing enough cesarean sections. However, the peer review process itself has not generated hard feelings. I am popular with the pediatric physician and nursing staff because our intrapartum policies have markedly reduced their visits to the operating room.

We did not address maternal morbidity in our study. However, it is well accepted that less morbidity occurs in patients who are delivered vaginally compared with those delivered by cesarean sections. Because of the reduction of almost 2000 cesarean sections during the past 3 years, we think that the decrease in post-cesarean section endomyometritis has substantially reduced overall maternal morbidity.

What do we do with patients with unknown scars? We have had patients from as far away as Nigeria whose medical records were more available that those of our local patients. It is embarrassing to note that the most difficult records to find are those from our own institution. When we first started with an aggressive approach to vaginal birth after cesarean section, patients with unknown scars were not allowed a trial of labor. Currently, we try to individualize management in these cases. We try to obtain a history as to the indication for the previous section. If the indication appeared to be an arrest of dilation at 8 cm (for example), then we conclude that the patient probably had a low transverse incision and therefore may proceed with a trial of labor.

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LETTERS TO THE EDITORS

HELLP does not always mean immediate HELP!

To the Editors: Dr. Sibai has presented his views on the HELLP syndrome (Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? AM J OBSTET GYNECOL 1990; 162:311-6). I argue that the disease presents in several patterns (A, B, C, . . .).[1] In my experience Native Americans and Hispanics have more liver involvement, blacks have more hypertension, and whites more thrombocytopenia. Definitions of the severity of HELLP syndrome according to absolute laboratory values will fail unless the ethnic background and disease pattern are considered.

After the introduction of screening laboratory tests in the mid 1960s, gravid women with unexpected elevated liver enzymes (serum glutamic oxaloacetic transaminase) and without severe hypertension were often treated as if they had viral hepatitis. Therapy was bed rest, diet, and isolation. Although "fulminating hepatitis" (probably HELLP) rarely developed in a patient, the majority did well. My article describing gravid women with no hypertension or mild hypertension, elevated liver enzymes, and thrombocytopenia as having preeclampsia was finally published after multiple changes of titles and with expansion of topics.[1] The pendulum then immediately swung to considering these same cases as having severe preeclampsia.[3] I have since seen patients who have been misdiagnosed in haste as having HELLP syndrome who in retrospect were seriously ill from idiopathic thrombocytopenia purpura, thrombotic thrombocytopenic purpura, or systemic lupus. Early delivery did not benefit them or their premature newborns.

I can find no evidence that maternal mortality or morbidity has improved since the introduction of the eponym "HELLP." I further believe that a diagnosis of HELLP syndrome is now a significant cause of iatrogenic prematurity and that many such patients <28 weeks' gestation should receive a trial of conservative (radical?) therapy. Dr. Sibai suggests that those who respond to plasma volume expansion, steroids, (aspirin), and bed rest are "without 'true HELLP' syndrome." I disagree. However, if calling the disease process "false HELLP" is necessary to achieve 1 to 2 extra weeks of intrauterine life, then false HELLP is a better term than all those I have tried.[1, 2-4]

The obstetrician's first duty is to the mother, but to burden the nursery and society with 25- to 28-week newborns on the premise that the mother with toxemia and laboratory abnormalities may be very ill[5] should be seriously debated.

Robert C. Goodlin, MD

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Reply

To the Editors: I thank Dr. Goodlin for his interest and comments regarding my article. This Clinical Opinion was designed to highlight some of the problems encountered in the diagnosis and management of this syndrome. Our patient population is either black or white; most patients with this syndrome are white. None of our patients are native Americans or Hispanics. Thus the ethnic background was considered in this report.

The reason that maternal mortality and morbidity has not improved is mainly related to failure to diagnose the disease and deliver the patient when appropriate.

Dr. Goodlin recommends conservative (radical?) therapy for patients with probable HELLP syndrome at 25 to 28 weeks' gestation. Our review of the literature and our data do not support benefit or the safety from such an approach. If such data are available, we encourage Dr. Goodlin to share this experience with the readers for the benefit of all. Until such data are published, I will continue to caution against conservative management in patients with true HELLP syndrome as described in my report.

Baha M. Sibai, MD

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Phenytoin and magnesium sulfate in eclampsia

To the Editors: In a recent excellent study on the use of intravenous phenytoin in severe preeclampsia (Ryan G, Lange IR, Naugler MA. Clinical experience with phenytoin prophylaxis in severe preeclampsia. AM J OBSTET GYNECOL 1989;161:1297-304), the authors suggest that this regimen may be effective in preventing eclampsia.

The results of our recent study[1] comparing the efficacy of phenytoin and intravenous magnesium sulfate in 22 cases of eclampsia do not support this statement.

None of the 11 patients managed with magnesium sulfate had further convulsions, whereas four of the 11 patients treated with phenytoin sodium had further convulsions despite therapeutic blood levels and were subsequently effectively treated with magnesium sulfate.

I would therefore suggest that the use of phenytoin in severe preeclampsia is not justified if this drug failed

to prevent further convulsions in four of 11 patients with eclampsia.

The indication for and the effectiveness of anticonvulsant therapy in the management of severe gestational proteinuric hypertension (preeclampsia) is unproved, and Redman[2] has stated that in most cases control of the hypertension and termination of the pregnancy will resolve the condition. This issue should be resolved by a large random control study.

J. Dommisse, FRCOG

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Reply

To the Editors: I welcome Prof. Dommisse's comments and I have read his recent article with great interest.[1] I acknowledge his concerns; however, for the following reasons I cannot agree with his conclusion that the use of phenytoin in severe preeclampsia is unjustified.

There will always be the occasional patient who has seizures regardless of the anticonvulsant used. This in itself is not reason enough to abandon that medication completely. Recurrent convulsions are reported in 26% of eclamptic patients who receive diazepam.[2] Treatment failures have also been reported with magnesium sulfate; seizures have occurred in 1% to 3% of patients despite therapeutic doses of magnesium sulfate.[3, 4] These reports stem from areas where magnesium sulfate is used quite liberally (9% of deliveries); thus the actual incidence of treatment failures in truly severe cases of preeclampsia may be much higher. Of more significance is the fact that 12% to 37% of cases of eclampsia occur in patients already receiving magnesium sulfate.[2, 4-6] In his own article Prof. Dommisse admits to a 3% incidence of recurrent convulsions in patients receiving magnesium sulfate in his institution.

The primary objection to use of magnesium sulfate is that it is unable to cross an intact blood-brain barrier and therefore has no central protective effect. Sibai et al.[7] have shown that the abnormal electroencephalographic pattern in eclampsia is unaffected by use of magnesium sulfate. An abnormal seizure pattern persists centrally despite the absence of any peripheral manifestation of a seizure, which is exactly what would be expected with the administration of a neuromuscular blocker such as magnesium sulfate.

Unlike status epilepticus,[8] almost all maternal mortality in eclampsia can be attributed directly to the cerebral manifestations of uncontrolled hypertension.[9-11] It has been suggested that aggressive management of hypertensive episodes is the key to prevention of seizures.[12, 13] The upper limit of cerebral autoregulation varies from individual to individual; thus we cannot set a universal level above which hypertension should be treated. It is possible that this may have been a significant element in several of the "phenytoin failures" described, especially since hypertension was not treated until it had reached a level of 115 mm Hg diastolic pressure.

I would be interested in further information regarding the patients in Prof. Dommisse's study who had recurrent seizures. This includes the timing of seizures in relation to the administration of clonazepam, the serum albumin levels, the levels of blood pressure compared with the other patients, and whether any other form of therapy, apart from magnesium sulfate, was given at the time of recurrence. I think the results of the neurologic investigation of these patients would also be enlightening, particularly with respect to diagnostic imaging and electroencephalographic studies. Most patients had already had multiple seizures before any therapy was given.

Our pharmacokinetic data would support his conclusion that an initial 500 mg intravenous phenytoin load, as used in the first half of his study, was inadequate. When we suggest using phenytoin at a 15 mg/kg dosage, the patient's weight is deduced from the most recent antenatal weight available. We do not actually weigh our patients before administration and did not intend to convey this impression. This approach has resulted in remarkably predictable blood levels.

As Prof. Dommisse points out, his results, although of concern, are not statistically significant. I appreciate the difficulty in convincing colleagues to try a new form of therapy instead of a well-established regimen, particularly when their initial experience with it is discouraging. I think it would be incorrect and premature to abandon the use of phenytoin in severe preeclampsia and eclampsia on the basis of preliminary results. There are several factors that individually or in combination may account for the imbalance noted.

I strongly support Prof. Dommisse's comment that a large randomized study is necessary. I suggest that such a study should consist of aggressive antihypertensive therapy throughout and include three protocols: magnesium sulfate, phenytoin, and no anticonvulsant, preferably with electroencephalographic monitoring in each group. It is hoped that such a study would put to rest the ongoing debate over which, if any, anticonvulsant should be used. Cape Town is one of the few units in the world where such a study would be feasible.

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Digoxin-like immunoreactive factor and respiratory distress syndrome

To the Editors: Digoxin-like immunoreactive factor, as measured with a commercial digoxin antibody assay (Stratus I, Dade, Miami), begins to appear in measurable amounts (>1.9 ng/dl) in serum of normal pregnant women at approximately the thirty-fifth week of pregnancy.[1] Newborn respiratory distress syndrome also becomes infrequent at this gestational age. I found that when the maternal serum digoxin-like immunoreactive factor level is <1.9 ng/dl, the newborn will likely have respiratory distress syndrome.

As shown in Table I, 18 patients who had amniocentesis at 32 to 39 weeks for determination of fetal lung maturity (lecithin/spingomyelin) had simultaneous maternal serum digoxin (digoxin-like immunoreactive factor) determinations by our clinical laboratory. A positive relationship was found (χ^2, $p < 0.02$).

Eleven patients were delivered by cesarean section between 29 and 31 weeks' gestation because of severe hypertension; all had received steroids, anticonvulsants, and antihypertensive agents. Only four mothers had serum levels of digoxin >0.2 ng/dl immediately before delivery and none of their infants had more than mild respiratory distress syndrome as diagnosed by our neonatologists. By contrast, the other seven patients with no detectable maternal serum digoxin-like immunoreactive factor (digoxin) were all delivered of infants with severe respiratory distress syndrome.

These cases support the concept but do not prove a causal relationship between maternal levels of digoxin-like immunoreactive factor and fetal lung development. Both the elevated digoxin-like immunoreactive factor and minimal respiratory distress syndrome could reflect responses to fetal stress in preterm deliveries.[1] In pregnant sheep, Liggins and Forester[2] found that fetal adrenal cortisol production modulated both the onset of labor and fetal lung development. It has been proposed that digoxin-like immunoreactive factor is a steroid, has an adrenal origin, and plays the same role in humans as does cortisol in fetal sheep.[1]

Table I. Eighteen cases with serum endoxin and amniotic fluid lecithin/sphingomyelin determinations (receiving no drug therapy)

Maternal serum endoxin (digoxin) value	*Amniotic fluid lecithin/sphingomyelin ratio*	
	>1.8	*<1.9*
>0.19 mg/dl	7	2
<0.20 mg/dl	0	9

Digoxin-like immunoreactive factor is in part bound to serum proteins, serum levels are depressed by drugs (steroids, antihypertensives, and tocolytic agents) and there is a need for a more specific test of pregnancy-related digoxin-like immunoreactive factor.[1] Despite these problems, studies should continue of digoxin-like immunoreactive factor in pregnancy complications.

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Dehydration-induced oligohydramnios

To the Editors: I read with interest the case report by Sherer et al. (Sherer DM, Cullen JBH, Thompson HO, Woods JR Jr. Transient oligohydramnios in a severely hypovolemic gravid woman at 35 weeks' gestation, with fluid reaccumulating immediately after intravenous maternal hydration. Am J Obstet Gynecol 1990; 162:770-1) in which severe nausea, vomiting, and diarrhea were associated with transient oligohydramnios. The authors attributed the oligohydramnios to maternal hypovolemia. However, the reactive nonstress test suggested that uterine blood flow was supplying adequate oxygenation to the fetal-placental unit.

I propose that maternal plasma hyperosmolality, rather than hypovolemia, resulted in the development of oligohydramnios. Although plasma osmolality was not measured at presentation, the plasma sodium level was elevated for pregnancy[1] and maternal urine sample demonstrated a potent antidiuretic response. Because

fetal plasma osmolality parallels maternal plasma osmolality (via transplacental flow), it is likely that a fetal antidiuretic response also was elicited. We have demonstrated that maternal dehydration (plasma osmolality increase of 10 mOsm) resulted in marked reductions in ovine amniotic fluid volume,[2] probably as a result of vasopressin-mediated reductions in fetal urine[3] and lung fluid production.[4]

These findings, together with the case report, illustrate the importance of maintaining adequate hydration during exercise, thermal exposure, or gastrointestinal losses in pregnancy.

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Reply

To the Editors: We appreciate Dr. Ross' comments concerning our case report and the opportunity to reply. Unfortunately we did not test maternal plasma and urine osmolality; however, plasma sodium, which was high for pregnancy, and low maternal urine specific gravity suggest an antidiuretic response that was appropriate for the severe maternal hypovolemic condition. We agree that maternal hyperosmolality could possibly be the underlying mechanism resulting in oligohydramnios. However, it would be difficult to differentiate between the independent effects of maternal hypovolemia and maternal hyperosmolality (and possible subsequent fetal hyperosmolality) in this case. Fetal antidiuretic hormone secretion is indeed a possible response to maternal hyperosmolality and may explain the oligohydramnios via a decrease in fetal urine output as suggested above.

A reactive nonstress test, although reassuring, does not in itself imply uterine blood flow supplying adequate oxygenation to the fetal-placental unit.[1,2] A contraction stress test might have exposed a partially compromised fetal-placental unit as a result of compromised uterine blood flow.[3] Because of prematurity, oligohydramnios, and the possibility of causing iatrogenic umbilical cord compression, we elected not to perform this test. Retrospectively, because of the reaccumulation of the amniotic fluid volume with correction of the maternal hypovolemia, further testing for fetal well-being was not necessary.

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A comment on thumbtacks for hemorrhage control

To the Editors: I read with interest the report by Patsner and Orr (Patsner B, Orr JW Jr. Intractable venous sacral hemorrhage: use of stainless steel thumbtacks to obtain hemostasis). Over the past 9½ years we have had occasion to use the thumbtack maneuver outlined in this article on two occasions. Both patients were undergoing extensive cytoreductive surgery. In both instances the venous bleeding could not be controlled by packing, clips, bone wax, or ligature. A steel thumbtack was used in each case and worked almost immediately. These are the only two instances in which we were in need of this "trick," so it is difficult to assess its efficacy.

Two caveats apply: First, not all thumbtacks are steel, and care must be taken not to use a metal that might corrode; second, when subsequent x-ray films are ordered for these patients, a panic-stricken call from the radiologist who is apt to be worried about the thumb-

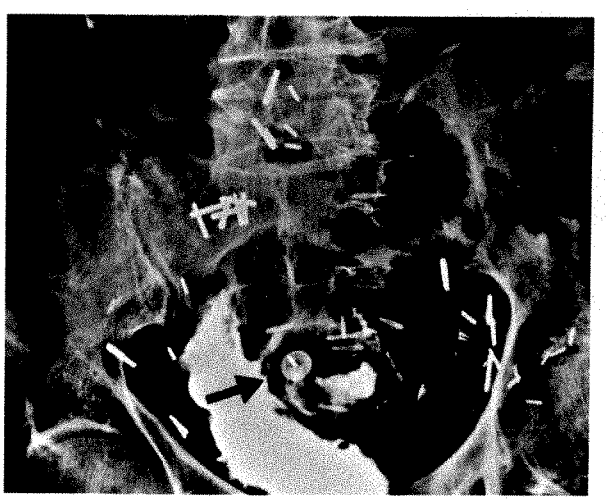


Fig. 1. Radiograph showing placement of thumbtack (PA).

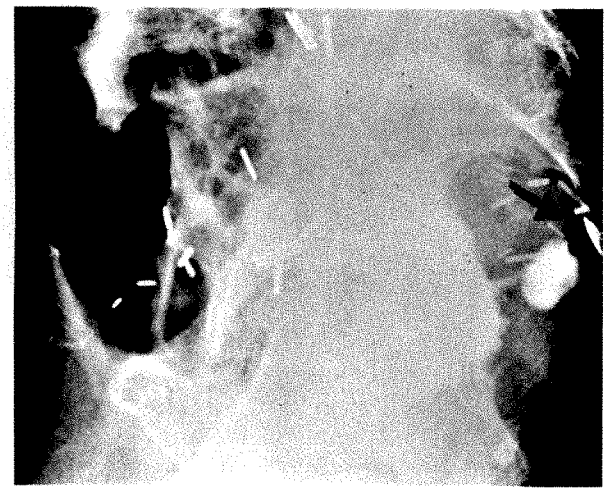


Fig. 2. Radiograph showing placement of thumbtack (lateral).

tack your patient ingested can be expected. Fortunately, as seen in the accompanying photographs, the lateral view clearly shows the placement of the tack in the sacrum.

I commend the authors for bringing more attention to this rarely needed but invaluable maneuver.

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Reply

To the Editors: Space limitations clearly prevented a comprehensive review of all the possible complications and requisite caveats that should accompany the use of stainless steel thumbtacks for control of presacral hemorrhage. Dr. Mann's points are both well taken: Only noncorrosive metals should be selected, and appropriate surgical history should be provided to radiologists as a matter of courtesy to avoid unnecessary confusion. (Of course, they might also be confused as to why anyone was still using wire to close incisions!)

Two additional points deserve mention. First, the risk for subsequent development of sacral osteomyelitis with this technique is unknown but must be kept in mind during patient follow-up. Second, although it would certainly be unusual to encounter (twice, no less) presacral venous plexus hemorrhage during cytoreductive surgery for ovarian cancer, Dr. Mann's two cases clearly illustrate that the technique may be required in situations other than elective presacral neurectomy.

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Early pregnancy failure—appropriate terminology

To the Editors: I was excited to see the title of the Clinical Opinion by Pridjianand and Moawad (Pridjian G, Moawad A. Missed abortion: still appropriate terminology? Am J Obstet Gynecol 1989;161:261-2). However, after carefully reading the article it appears that even the new terms they recommend are already outdated.

I concur that advances in ultrasonography have changed our concepts about early pregnancy failure. Until recently, the accepted ultrasonographic definition for "missed abortion" was a crown-rump length of 15 mm without evidence of cardiac activity.[1] A "blighted ovum" or anembryonic pregnancy was a gestational sac ≥25 mm mean sac diameter without an embryo.[2] The introduction of the vaginal probe has allowed a high degree of resolution in spite of magnification. This results in a form of "sonomicroscopy" wherein structures that cannot be seen with the naked eye can be imaged. Investigators have reported seeing a cardiac signal with M-mode technology before being able to image the actual embryo.[3] This should not be surprising since the embryonic disc, amnion, and yolk sac are present even in the early gestational sac. They are simply too small to be imaged even with the sonomicroscopy capability currently available. Therefore the classic distinction between blighted ovum and missed abortion becomes blurred. Most anembryonic pregnancies are not truly without embryos. They simply lose viability before our ability to image them. Furthermore, in many cases there is initial early embryonic development with subsequent loss of viability and then embryonic resorption.[4] This then ultimately results in the sonographic appearance of an "empty sac."

I agree with the authors that there may be different causes for intrauterine pregnancy failure. Certainly, the earlier it occurs, the more likely it is related to chromosomal polyploidy, whereas in later failures abnormalities of implantation, placentation, associated fibroids, or infection may be causative. I applaud the authors' attempt to update terminology but I would suggest that they go even further as outlined above.

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Response declined

Conservative management of cervical pregnancy with subsequent fertility

To the Editors: I read the article by Bachus et al. in the February, 1990, issue with great interest (Bachus KE,

Stone D, Suh B, Thickman D. Conservative management of cervical pregnancy with subsequent fertility. AM J OBSTET GYNECOL 1990;162:450-1). However, I question the wisdom of performing suction curettage in the patient mentioned in the article.

As reported, this procedure resulted in violent hemorrhage. Fortunately, in this patient the profuse hemorrhage that resulted in reduction of hematocrit from 38% to 28%, despite administration of packed red blood cells, was controlled by the means described by the authors. Not every patient with this problem is a candidate for suction curettage because this procedure may result in not only violent hemorrhage as described by the authors, but also life-threatening hemorrhage with inherent severe medical and legal complications. I respectfully disagree with the statement that "this approach should be considered a standard of care in those patients desiring future fertility." This may imply that the clinician may perform suction curettage in all such patients, which frankly may result in severe and life-threatening hemorrhage.

I would like to propose that medical rather than surgical management of these patients may be lifesaving in this condition. The administration of methotrexate into the gestational sac or systemic use of methotrexate, which is successfully used in tubal and cervical pregnancy, is an excellent medical approach. Methotrexate, 1 mg/kg, alternating on a daily basis with folinic acid, 0.1 mg/kg (total of four doses) has been suggested. In their report Oyer et al.[1] used only two doses of the above regimen and successfully treated cervical pregnancy without the occurrence of severe hemorrhage. These drugs should be used only if serum transaminase and other laboratory test results are normal.

In summary, individualization of patients with cervical pregnancy who wish future fertility is in order, and a decision should be made whether a surgical approach or medical treatment is indicated, as outlined above, for the best management for such patients.

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REFERENCE

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Reply

To the Editors: We thank Dr. Ayromlooi for his interest in and comments concerning our article. This allows further discussion about treatment options for this interesting, yet sometimes terrifying condition.

When we stated that this approach be considered a standard of care in those patients desiring future fertility, we were referring to conservative means of management as opposed to hysterectomy. The purpose of this article was not necessarily to advocate surgical means of treatment compared with methotrexate therapy, but in light of Dr. Ayromlooi's comments that "medical rather than surgical management of these patients may be lifesaving," we think that a more complete description of the benefits, risks, and outcomes of these two methods is necessary.

It is apparent from the cases in the literature, that most cases of cervical pregnancy are not diagnosed preoperatively.[1, 2] Clinicians perform curettage for what is thought to be an incomplete or inevitable abortion only to encounter the hemorrhage associated with this rare form of ectopic pregnancy. Obviously, in this situation mechanical packing or surgical therapy are the only methods available, and familiarity with the method described can avoid significant morbidity. A large Foley balloon, with or without adjunctive cerclage, can be applied expeditiously to control hemorrhage. Its effectiveness has been reported[3, 4] and avoids the need for more extensive surgery such as internal iliac artery ligation or hysterectomy.

The "wisdom of performing suction curettage" in this patient because of the inherent hemorrhage potential is questioned by Dr. Ayromlooi. The concern is that if performed in all patients with cervical pregnancy, life-threatening hemorrhage may result. Admittedly, curettage of this form of ectopic pregnancy does carry a risk of significant hemorrhage because of the poor contractile properties around the implantation site within the cervix and transfusion of up to 6 units has been reported.[5] Despite the blood loss, none of the patients reported who were treated by the techniques described in our report have required more definitive therapy. It is hoped that increased early detection of cervical pregnancy by clinical and ultrasonographic methods will result in preoperative preparation that will reduce the need for transfusion.

This hemorrhage, however, is not unique to surgical management as Dr. Ayromlooi implies. Medical management with methotrexate also has similar bleeding potential. Of the 10 patients with cervical pregnancy treated with methotrexate reported in the literature, two had reports of large hemorrhages that ultimately led to hysterectomy.[2] Furthermore, these bleeding episodes occurred up to 18 days after methotrexate therapy.[2, 6] This is disconcerting because the patient at this point may already be home. One additional patient required hysterectomy for persistence of the cervical mass after this medical therapy,[7] and one patient had hemorrhage that ultimately was controlled with adjunctive use of internal iliac ligation and intracervical balloon tamponade.[8]

This medication also carries a risk of toxicity that cannot be ignored. Stomatitis and elevated serum transaminase levels limited therapy in two of the reported 10 cases.[7, 9] In fact, the patient in the case cited by Dr. Ayromlooi had methotrexate use discontinued after two of the four planned doses because of hepatic toxicity.[9]

We agree that not all patients with cervical preg-

nancy are candidates for conservative treatment modalities. Some authors have recommended limiting attempts to conserve the uterus to the first 8 weeks of pregnancy.[10, 11] This may be particularly true for those patients treated with methotrexate, because one of five patients treated within the first 8 weeks required additional therapy to control hemorrhage.[2] Beyond 8 weeks, two of three cases required surgical intervention for control of bleeding.[7, 8] Although the numbers are still small, this trend is similar to the experience with methotrexate in treating tubal ectopic pregnancies in which excessive size and high human chorionic gonadotropin titers have been shown to have poorer outcomes.[12, 13] Currently, experience with contemporary conservative treatment methods beyond the first trimester is extremely limited.

Choice of the optimal treatment for a patient who wishes to preserve fertility is difficult. It should be recognized that both of these treatment modalities have inherent morbidities that must be considered by the patient and the physician when selecting a conservative treatment plan.

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Can shoulder dystocia be prevented?

To the Editors: Although the recent article by O'Leary and Leonetti (O'Leary JA, Leonetti HB. Shoulder dystocia: prevention and treatment. AM J OBSTET GYNECOL 1990;162:5-9) was published in the Clinical Opinion section, I am concerned that some of the statements might be misconstrued. The third sentence in the paper implies that many shoulder dystocias can be prevented by quoting a source that states that many shoulder dystocias can be anticipated. Any algorithm to predict shoulder dystocia should include an estimation of the number of falsely alarming predictions of damage to the infant. In other words, how many "unnecessary" cesarean deliveries are necessary to prevent each case of shoulder dystocia?

The suggestion that "once a shoulder dystocia, always a cesarean" obviously ignores the fact that there are complicated dynamics that predict whether shoulder dystocia will occur. Just as the necessity for a prior cesarean delivery for management of cephalopelvic disproportion poorly predicts the need for subsequent cesarean delivery for the same indication, in the absence of more compelling data we should not accept the thought that shoulder dystocia will predictably repeat itself.

Finally, the order of suggested treatment of shoulder dystocia that the authors propose in Table IV is certainly debatable; however, I would suggest that the maneuvers begin with the least invasive, that is, the McRoberts maneuver. Proceeding with a list as suggested is sensible, although I still am concerned about the suggestion that the head can be forcibly replaced with safety. Although this may be an appropriate procedure in the authors' hands, multisite performance in more patients will make me (and many others) feel more comfortable.

Whereas it is certainly true that increasing the cesarean section rate will, as the authors propose, reduce the incidence of shoulder dystocia, it will also increase the incidence of maternal morbidity and mortality. I hope that we can balance these risks in adopting a safe and sane standard for the management of this uncommon, but frightening and potentially disastrous complication of pregnancy.

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Reply

To the Editors: We appreciate Dr. Nagey's thoughtful and meaningful remarks. It is hoped that by raising the level of anticipation of shoulder dystocia a more thorough clinical assessment would allow the physician to accumulate more data and thus recognize more risk factors for shoulder dystocia (i.e., the flat pelvis).

The expression "once a shoulder dystocia, always a cesarean" is based on the assumption that the same set

of clinical parameters is operative at the time of the next delivery (e.g., macrosomia, glucose intolerance).

To date, 34 cases of cephalic replacement have been collected from around this country with only one failure and one major maternal complication. We agree that the McRoberts maneuver is most effective.

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Measurement of cardiac output with impedance cardiography

To the Editors: An interesting article was published in the September 1989 issue of the JOURNAL (Masaki DI, Greenspoon JS, Ouzounian JG. Measurement of cardiac output in pregnancy by thoracic electrical bioimpedance and thermodilution. AM J OBSTET GYNECOL 1989;161:680-4) concerning the measurement of cardiac output in patients with cardiac problems, pancreatitis, septic shock, and pregnancy-induced hypertension. More than 10 years ago, in 1978, we investigated cardiac output and stroke volume index in pregnant women with threatening premature birth compared with normal pregnancies in the standing, supine, and left lateral positions using a Minnesota impedance cardiograph. We found a statistically highly ($p < 0.005$) significant reduction of cardiac output in the standing position in patients with premature labor that disappeared in the lying positions and a significant ($p < 0.025$) reduction in stroke volume, which disappeared in the supine position but persisted in the left lateral position.

The absolute values of cardiac output were in the same range as in the investigations by Masaki et al.

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Response declined

Labor epidural analgesia and dystocia-related cesarean section

To the Editors: Does labor epidural analgesia increase the need for obstetric intervention? Most published studies addressing this question, some that implicate and others that exonerate labor epidural analgesia, have design flaws. The same is true of two recent reports claiming that labor epidural analgesia increases the rate of dystocia-related cesarean section.[1, 2] In the first, parturients chose their methods of pain relief and altered it at will.[1] In the second report involving "matched" subjects, the anesthesiologist and obstetrician prescribed analgesia.[2] Furthermore, their patients were not matched for height and weight, factors that are likely to influence pelvic bony and soft tissue anatomy.[3]

Thorp et al.[1] argue that a controlled, randomized comparison between labor epidural analgesia and parenteral narcotics would be unethical and liable to patient dropout.[1] However, Philipsen and Jensen[4] have prospectively compared labor epidural analgesia and intramuscular meperidine in a randomized study and found no differences in obstetric interference rates. Cesarean section was performed for management of cephalopelvic disproportion in nine of 10 and three of six parturients, and malrotation was present in three of nine and none of a group of three patients, respectively. Their cesarean section rates (labor epidural analgesia, 7.8% or 4/51 and meperidine, 5.9% or 3/51) are thus commensurate with those of others.[1]

Thorp et al.[1] gave patients a bolus dose of 0.25% bupivacaine and infused 0.125%. Diro and Beydoun[2] and Philipsen and Jensen[4] used intermittent injections of 0.25% and 0.375% bupivacaine, respectively. Lamont et al.[5] compared bupivacaine infusion with intermittent "top-ups" but "allowed a passive phase of second stage of up to 3 hours in each group." Newer labor epidural analgesia techniques that offer optimal maternal analgesia without muscle weakness, and loss of perineal pressure sensation[6-8] may thus favor spontaneous vaginal delivery.

Thorp et al.[1] stress the current medicolegally inspired reluctance of some obstetricians to use forceps. Are their results perhaps related more to obstetric preference rather than labor epidural analgesia? Diro and Beydoun[2] delivered nine patients who had received epidural anesthesia with forceps, within 2 hours of reaching 10 cm dilatation. Prolonging the second stage up to 3 hours might have changed the clinical situations.[5]

Forty percent of nulliparous women suffer severe pain with childbirth.[9] This may jeopardize the fetus.[10, 11] Labor epidural analgesia provides maternal analgesia with improved transplacental exchange.[12, 13] A large, controlled, prospective multicenter study incorporating newer labor epidural analgesia and labor management techniques[6-8] could resolve the issue.[14, 15] Patients could be randomized to receive either labor epidural analgesia with intravenous saline solution or intravenous meperidine with epidural saline solution, allowing escape to labor epidural analgesia for unbearable pain. When the grave accusations being leveled at labor epidural analgesia are considered,[1, 2] this approach would be ethical in our view.

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Pemphigus in pregnancy

To the Editors: We read with interest the report by Kanwar et al. of another case of pemphigus vulgaris in pregnancy (Kanwar AJ, Kaur S, Abraham A, Nanda A. Pemphigus in pregnancy. AM J OBSTET GYNECOL 1989;161:995-6). We heartily support the authors' conclusion that "it is important that physicians and obstetricians be aware of the problem" and "consider as problematic the treatment of pemphigus during pregnancy." Pemphigus vulgaris during pregnancy that affects the fetus is very rare. The authors erroneously mentioned 48 such cases[1]; however, this figure also includes cases of pemphigus foliaceus, which does not affect the neonate and thus does not pose a difficult therapeutic problem during pregnancy.

We did express our opinion[2] that pemphigus vulgaris may severely endanger the fetus because the stillbirth rate for the reported infants born to mothers with this immune-mediated disease during pregnancy is 23%. This is probably a result of the effect of treatment. It may be the result of high doses of corticosteroid therapy, masking a possibly overwhelming infection or causing placental insufficiency. We might find support for this in the report by Kanwar et al. of a newborn with a birth weight of 1800 gm at 36 weeks' gestation, who was obviously small for gestational age, possibly because of placental insufficiency, after the mother had been treated with 60 mg prednisolone per day for some time.

We recommend repeated plasmapheresis as an alternative treatment to improve the precarious state of a patient or fetus with pemphigus vulgaris, thus avoiding high doses of corticosteroids when a high titer of circulating pemphigus antibodies is present.[3] Plasmapheresis should contribute to the alleviation of risk to the infants of pregnant women with pemphigus vulgaris.

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2. Merlob P, Metzker A, Hazaz B, Rogovin H, Reisner SH. Neonatal pemphigus vulgaris. Pediatrics 1986;78:1102-5.
3. Metzker A, Merlob P. Pemphigus in pregnancy: a reevaluation of fetal risk. AM J OBSTET GYNECOL 1987;157: 1012-3.

Reply

To the Editors: We thank Drs. Metzker and Merlob for their comments on our article. Although we did mention that only 48 patients in whom pemphigus developed or who had recurrent pemphigus during pregnancy have been reported in the literature, it was not specified that all these cases were of pemphigus vulgaris. Because transplacental transfer of IgG antibodies does occur in pemphigus, why pemphigus foliaceus does not affect the newborn is a matter of conjecture. The milder form of the disease, low levels of circulating antibodies, and smaller doses of corticosteroids required for control of the disease perhaps protect the fetus.

We do not agree with their suggestion that repeated plasmapheresis is an alternative treatment to improve the precarious state of a patient or fetus with pemphigus vulgaris. At best plasmapheresis is still an experimental procedure in treatment of pemphigus and its use is presently restricted to severe corticosteroid-resistant cases of pemphigus.[1,2] In our opinion it is not worthwhile to subject the mother and fetus to the extensive stress of this repeated procedure with the risks and ill effects of its own.

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Graphic mnemonic for variable decelerations

To the Editors: Our hospital uses the system of Kubli et al. (Kubli FW, Hon EH, Khazin AF, Takemura H. Observations on heart rate and pH in the human fetus during labor. AM J OBSTET GYNECOL 1969;104:1190-206) to classify the severity of variable fetal heart rate decelerations. However, the definitions can be cumbersome to memorize and recall. I have found the following graphic mnemonic very helpful in teaching on rounds.

Picture a graph divided into nine zones by four lines, as in Fig. 1. The horizontal axis represents the duration of the deceleration. The vertical axis represents the lowest level to which the heart rate drops.

Locate the point that characterizes the deceleration in question. If the point falls within the lower right-hand zone, the deceleration is severe. If the point falls within the two zones adjacent to the severe zone, the deceleration is moderate.

Thus it is only necessary to remember the zone locations and the values determining the four lines.

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A conceptual thought

To the Editors: The article by Einarson et al. (Einarson TR, Koren G, Mattice D, Schechter-Tsafriri O. Maternal spermicide use and adverse reproductive outcome: A meta-analysis. AM J OBSTET GYNECOL 1990;162:655-60) reminded me of a (probably) quixotic semantic crusade for 1990. When something happens before pregnancy, it's *preconceptional.* When something happens before thinking, it's *preconceptual.* Yes, yes, I know pregnancy sometimes happens without thinking.

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Response declined

Stability of human chorionic gonadotropin and its α-subunit

To the Editors: We were pleased to read that Petrocik et al. (Petrocik E, Wassman ER, Kelly JC. Prenatal screening for Down syndrome with maternal serum human chorionic gonadotropin levels. AM J OBSTET GYNECOL 1989;161:1168-73) confirmed our findings[1]

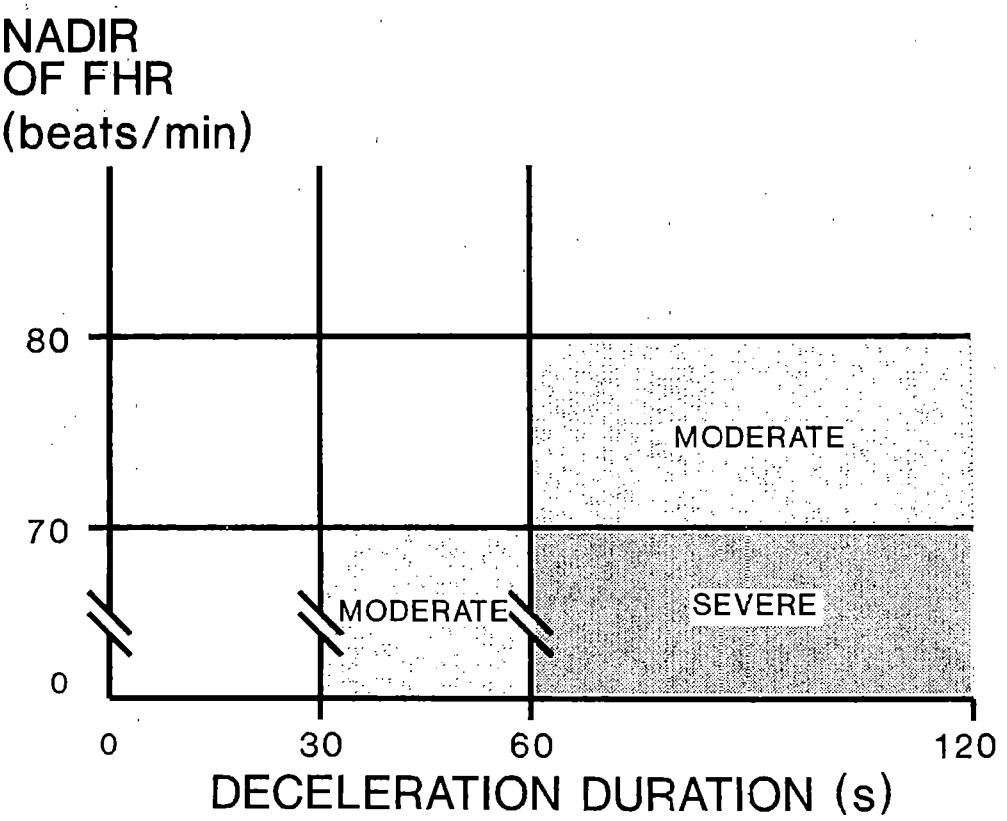


Fig. 1. Graphic mnemonic for identifying the severity of variable decelerations.

on the remarkable stability of the α-subunit of human chorionic gonadotropin in unfrozen whole blood and unfrozen and frozen serum and plasma samples. However, the authors regrettably implied (in the third sentence, second paragraph, second column on page 1172) that we had not studied the stability of the whole human chorionic gonadotropin molecule and that their study now investigates this deficiency. We would like to point out that our published article does in fact also contain data on the stability of the whole human chorionic gonadotropin molecule. We are pleased that Petrocik et al. also confirmed this aspect of our published study.

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REFERENCE

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Response declined

Vaginal probe ultrasonography and ectopic pregnancy

To the Editors: It was with great interest that I read the article by Stiller et al. (Stiller RJ, deRegt RH, Blair E. Transvaginal ultrasonography and patients at risk for ectopic pregnancy. AM J OBSTET GYNECOL 1989;161: 930-3). I agree with their conclusions about the advantages of the vaginal probe and its combination with the determination of a quantitative human chorionic gonadotropin level will allow the majority of patients to be offered a definitive diagnosis at initial evaluation or within 48 hours. However, I would like to make two additional points that I think would further enhance the clinical usefulness of their technique.

First, the use of curettage in examination of unstained material with low-power magnification will be an appropriate next step in triage for certain patients.[1] This will pertain when the human chorionic gonadotropin levels rise at a subnormal rate of rise or when the human chorionic gonadotropin level exceeds a definitive discriminatory zone as established by one's own laboratory. Such cases may represent failing intrauterine pregnancies or possibly ectopic pregnancy, and performance of curettage and examination of tissue to distinguish villus material from maternal decidua can be a valuable next step in the triage of such patients. Such a procedure would have prevented the unnecessary laparoscopy performed in their cited case in which misdiagnosis of an intrauterine gestation occurred.

Second, it is unfortunate that some authors have chosen to use the "double decidual sac" sign[2] as the ultrasonographic proof of an intrauterine pregnancy. There is ample evidence that the echogenic "rind" around the sonolucent center that is visualized is not the result of two layers of decidua being fused; rather, the primary trophoblastic villi, as they come off the chorionic membrane, invade maternal decidua and produce a trophoblastic decidual reaction that is highly echogenic. The chorionic cavity is fluid filled, contains the embryonic complex, and is sonolucent. Initially the primary villi are very homogeneous (they have not yet begun to branch and proliferate), and as they invade maternal decidua they produce the classic echogenic "rind" around the sonolucent chorionic cavity to which the authors refer. Outside the uterus (ectopic pregnancy), the echogenicity is a result of primary villi invading decidualized tubal endothelium. Unfortunately, the authors, who have obviously done high-quality ultrasonography with modern vaginal ultrasonographic equipment, have chosen an 8-year-old article in which research was done transabdominally to describe the anatomic landmarks that they chose to follow.

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2. Bradley WG, Fiske CE, Filly RA. The double sac sign of intrauterine pregnancy: use in exclusion of ectopic pregnancy. Radiology 1982;143:223-7.

Reply

To the Editors: I appreciate the comments on our article. I agree that there may be some circumstances in which examination of uterine contents for the presence of chorionic villi may be useful in the differentiation of the failing intrauterine pregnancy from the ectopic pregnancy. Admittedly, this would have been useful in one case in our original series; however, in more than 50 patients with ectopic pregnancies seen subsequently, we have not needed to perform curettage for evaluation of chorionic tissue to confirm pregnancy location appropriately.

With regard to the criticism of the term "double decidual sac sign" used in our article, it must be noted that the description of an anechoic area surrounded by an echogenic rind has been widely accepted in the ultrasound literature as definitive evidence of a gestational sac, and it is for this purpose that the term was used. I would also assume that it was for similar reasons that Dr. Goldstein used this same term in his article

published only 2 months before the submission of our article.[1]

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REFERENCE

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A convenient method to identify prior surgical procedures

To the Editors: Current standards of practice mandate adequate documentation of medical care. Such standards derive in part from legal concerns but increasingly, obstetric and gynecologic care is often predicated on an adequate disclosure of a patient's prior medical and surgical history. As examples, repeat cesarean sections may be avoided and a trial of vaginal delivery attempted if documentation of a lower uterine segment incision can be made.[1] Similarly, tubal reanastomoses may be scheduled based solely on a review of the operative report describing the type of tubal ligation, thereby avoiding the cost and risk of laparoscopy.[2] However, the mobility of our population, particularly evident in the military services, frequently results in a fragmented medical record, and the question remains with regard to exactly what sort of care had previously been rendered.

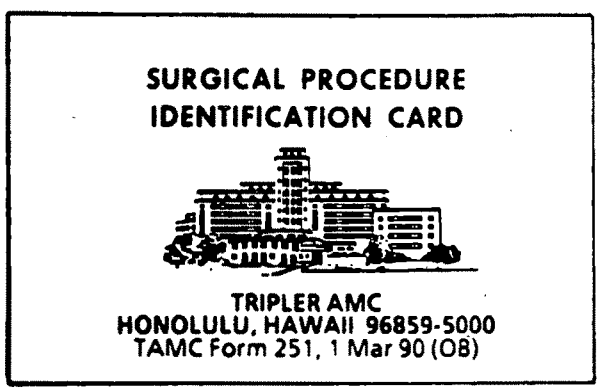


Fig. 1. Identification card for surgical procedures.

The concept of personally carried medical records is one potential solution and in fact is not new to obstetrics and gynecology. A cumulative, hand-carried obstetric record *(mutterpass)* is common practice in the Federal Republic of Germany, and a pocket identification card has been used in the gynecologic population to document the placement of an intrauterine contraceptive device. We extended this concept to surgical procedures and designed an identification card to document the type of either cesarean section or tubal surgery (Fig. 1). The card provides space for identification of the type and date of the procedure and is similar in size to a standard credit card. On the reverse side, we chose to display a sketch of our medical center and our address, although any logo(s) or private practice name(s) could be depicted. We currently distribute the card to any patient who has either delivery by cesarean section, tubal ligation, or tubal surgery when the risk of ectopic pregnancy is increased. Use of this card should provide a convenient and immediate means to document prior surgical care, especially in emergent circumstances, and may be used while awaiting formal medical records and operative reports.

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Fetal Doppler velocimetry in twins

To the Editors: Divon et al. (Divon MY, Girz BA, Sklar A, Guidetti DA, Langer O. Discordant twins—A prospective study of the diagnostic value of real-time ultrasonography combined with umbilical artery velocimetry. AM J OBSTET GYNECOL 1989;161:757-60) performed umbilical artery velocimetry with a continuous-wave Doppler system and stated that the presence of either a 15% difference in ultrasonographic estimates of fetal weight or a 15% difference in systolic/diastolic ratios correctly identified 78% of discordant pairs. With a pulse-wave Doppler-duplex system enabling accurate sampling of vessel because of its depth resolution, we have shown[1] that from ultrasound criteria and Doppler study of the umbilical and fetal internal carotid arteries, decreased fetal internal carotid artery pulsatility index (cutoff value ≤ 1.2) was found to be the best predictor of twin discordancy (sensitivity 83%, specificity 95%, positive predictive value 91%, negative predictive value 91%). Pulsatility index determination provides direct

evidence of the brain-sparing effect in the growth-retarded fetus.[2, 3]

The umbilical artery Doppler assessment may present problems in twin gestations because it is not always easy to verify which fetus is associated with the umbilical vessel under study.

Our findings suggest that it may be more practical to use ultrasonographic weight estimation below the 10th percentile (sensitivity 67%) or below the 25th percentile (sensitivity 92%) as a screening tool and then perform Doppler studies to determine the twin fetus at risk. With these sequential tests the specificity is improved (91%, 98%) at the expense of reduced sensitivity (56%, 76%, respectively).

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Reply

To the Editors: We appreciate the interest of Dr. Degani in our recent article. As suggested, umbilical artery velocimetry studies are occasionally difficult in twin gestation. Pulsed-wave, duplexed devices may provide some help; however, we do not think that these devices can establish with certainty the association between the umbilical cord and the fetus.

Our experience with discordant twins indicates that a combined analysis of both Doppler velocimetry and estimated fetal weight yields superior results to these obtained by initial analysis of the differences between fetal weights. Therefore we see no need for a "two-step" diagnostic approach.

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Ketoconazole treatment of Cushing's syndrome in pregnancy

To the Editors: I was most interested to read the useful and comprehensive review of Cushing's syndrome and pregnancy by Aron et al. (Aron DC, Schnall AM, Scheeler LR. Cushing's syndrome and pregnancy. Am J Obstet Gynecol 1990;162:244-52).

Experience with medical therapy has been extremely limited. Ketoconazole blocks 11β-hydroxylase, 17α-hydroxylase, and cholesterol side-chain cleavage in adrenal steroidogenesis and has been useful in the control of hypercortisolism, although it is teratogenic and embryotoxic in animals.

Amado et al.[1] recently reported the use of ketoconazole in a woman with deteriorating Cushing's syndrome caused by an adrenal adenoma from 32 weeks' gestation until 36 hours before cesarean section at 37 weeks. The clinical and biochemical response was excellent. Cortisol and aldosterone levels decreased, the level of 11-deoxycortisol increased, and there was no diminution in the levels of either estradiol or progesterone; a normal healthy female infant was delivered and remained well after 18 months.

Obviously, "one swallow doesn't make a summer," but their work deserves further investigation.

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REFERENCE

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Response declined

Vaginal birth after abdominal delivery

To the Editors: We would like to comment on the article by Yetman and Nolan (Yetman TJ, Nolan TE. Vaginal birth after cesarean section: A reappraisal of risk. Am J Obstet Gynecol 1989;161:1119-23). The authors conclude that successful vaginal birth after cesarean section carries a higher risk for significant perineal lacerations. This conclusion cannot be drawn from the data presented because the authors do not report the number of episiotomies used for delivery within the study and control groups. Because midline episiotomy predisposes the anal sphincter and rectum to injury,[1-4] a higher incidence of episiotomy in either group could have confounded the results.

The combination of vaginal vault lacerations, cervical lacerations, and third- and fourth-degree lacerations under the single heading of perineal lacerations is also misleading. These four separate categories of birth canal trauma should have been analyzed separately. Whether the incidence of any of these individual lacerations would have been different between the control and study groups by a statistically significant margin cannot be ascertained from the data as published. This is important because the authors draw attention to rectovaginal fistula as a potentially serious consequence of "perineal lacerations." However, rectovaginal fistulas are the occasional consequence of fourth-degree perineal lacerations but not of cervical, vaginal vault, or third-degree lacerations. Similarly, it would be important to know if cervical lacerations were significantly more common in the study group, because cervical lac-

erations may predispose patients to incompetent cervix in future pregnancies. In short, combining the several types of perineal lacerations may have contributed to the data achieving statistical significance, but it confuses the really important clinical issues.

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Response declined

Corticotropin-releasing hormone in amniotic fluid

To the Editors: I read with great interest the article by Sasaki et al. (Sasaki A, Shinkawa O, Yoshinaga K. Immunoreactive corticotropin-releasing hormone in amniotic fluid. AM J OBSTET GYNECOL 1990;162:194-8). The authors stated that their article is the first report on the presence of corticotropin-releasing hormone in amniotic fluid, but we remind readers that in 1988 we published an article on corticotropin-releasing hormone in human amniotic fluid in the JOURNAL.[1] We found a concomitant increase of corticotropin-releasing hormone and cortisol levels in amniotic fluid with advancing gestation and increased concentrations of corticotropin-releasing hormone in pregnancies complicated with preeclampsia and fetal intrauterine growth retardation. We speculated that increased intrauterine release of corticotropin-releasing hormone in preeclampsia may be of placental origin and may stimulate fetal pituitary-adrenal axis and promote the process of fetal maturation in obstetric stress. In addition to the placenta, the amnion may be a potential source of corticotropin-releasing hormone in amniotic fluid because we have found an intensive immunostaining of corticotropin-releasing hormone in this tissue.[2]

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REFERENCES

1. Laatikainen TJ, Räisänen IJ, Salminen KR. Corticotropin-releasing hormone in amniotic fluid during gestation and labor and in relation to fetal lung maturation. AM J OBSTET GYNECOL 1988;159:891-5.
2. Saijonmaa O, Laatikainen T, Wahlström T. Corticotropin-releasing factor in human placenta: localization, concentration, and release in vitro. Placenta 1988;9:373-85.

Reply

To the Editors: We have carefully considered the criticisms raised by Dr. Laatikainen and appreciate the opportunity to clarify some aspects of our study.

We believe it is important to characterize the total immunoreactive materials precisely by gel filtration or high-pressure liquid chromatography, if the presence of corticotropin-releasing hormone in amniotic fluid is to be proved. The presence of total immunoreactivity does not indicate the presence of biologic or intact corticotropin-releasing hormone molecule. Indeed, we found 60% of total corticotropin-releasing hormone—like immunoreactivity in amniotic fluid was authentic corticotropin-releasing hormone molecule and the remaining 40% was smaller fragment. In this regard our article was the first report on the presence of authentic corticotropin-releasing hormone in human amniotic fluid. The physiologic significance of corticotropin-releasing hormone in amniotic fluid is not yet known. We doubt Dr. Laatikainen's speculation that corticotropin-releasing hormone in amniotic fluid may stimulate the fetal pituitary-adrenal axis and promote fetal maturation. Corticotropin-releasing hormone levels in amniotic fluid are not high enough to promote its biologic activity, and it is also unclear what type of route is present from amniotic fluid to fetal pituitary gland. We previously purified placental corticotropin-releasing hormone and its partial structure was identical to rat corticotropin-releasing hormone.[1] Maternal plasma corticotropin-releasing hormone levels during late pregnancy are extremely high,[2] and the fetal plasma corticotropin-releasing hormone level is 100 times less than that of the maternal level. Corticotropin-releasing hormone present in maternal peripheral plasma is biologically active and its level is two times higher than that of hypothalamic-portal plasma in rats. Therefore, we conclude that placental corticotropin-releasing hormone is primarily secreted into maternal plasma and has a role in stimulation of the maternal pituitary-adrenal axis during pregnancy.[3] Currently there is no direct evidence whether it may have a function to the fetal side. Finally, the precise origin of corticotropin-releasing hormone in amniotic fluid is not clear; we have already discussed several possibilities regarding its origin. The amnion may be the origin if corticotropin-releasing hormone is present as indicated by immunostaining. However, we also emphasize that immunostaining studies sometimes produce pitfall results.[4]

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Ultrasonographic dating of very early pregnancy

To the Editors: How does one date a normal singleton intrauterine pregnancy ultrasonographically before detection of the crown-rump length[1] or early fetal cardiac activity[2]?

We attempted to answer this question in 1984 by relating the mean gestational age to mean sac diameter.[3] Since then we have used the following simple formula[4] for dating several hundred early normal singleton intrauterine pregnancies and have found it to be reliable and useful with mean sac diameters ≤15 mm by either transabdominal[2, 3] or transvaginal techniques: Mean gestational age in days = 30 + Mean sac diameter in millimeters (i.e., 5 mm sac = 35 days). The 95% confidence limits are ±3 days, assuming the pregnancy is normal.

The mean gestational age is menstrual age (conceptional age + 2 weeks). The mean sac diameter is obtained by averaging the length, width, and depth on perpendicular ultrasonograms through the largest portion of the gestational sac. All measurements should be from sac-fluid to fluid-sac interfaces.[2, 3]

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REFERENCES

1. Robinson HP, Fleming JEE. A critical evaluation of sonar crown-rump length measurements. Br J Obstet Gynaecol 1975;82:702-10.
2. Cadkin AV, McAlpin J. Detection of fetal cardiac activity between 41 and 43 days of gestation. J Ultrasound Med 1984;3:499-503.
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Maternal exercise and early pregnancy outcome

To the Editor: We enjoyed the article by Dr. Clapp on maternal exercise and early pregnancy outcome (Clapp JF. The effects of maternal exercise on early pregnancy outcome. Am J Obstet Gynecol 1989;161:1453-7). It adds to the growing body of literature that supports the position that judicious antigravitational exercise before and during pregnancy does not adversely affect outcome.

We agree that the power of his experimental design would increase with wider representation of the populace. Cross-cultural parameters may also be considered variables. Furthermore, a cross-sectional/longitudinal approach based on percentages of body fat versus level of exercise over a 24-month period would provide data on changes of body fat and levels of exercise before and during pregnancy versus outcome. In this way control over possible experimental bias would be increased.

Because the reliability of uncollaborated self-reporting has been shown to be low, efforts should be made to collaborate all reports of duration and intensity of exercise per day.

Further strength of design can be accomplished by controlling variances in diet. Records of quality and quantity of calories consumed during every 24-hour period would provide another axis of data by which possible dietary influences on pregnancy outcome may be made apparent.

Another possible effect may lie in unaccounted for physiologic changes that can occur when a usually active woman ceases all forms of exercise when she becomes pregnant. Thus a comparison between exercise before and during pregnancy, exercise before but not during pregnancy, and pregnancy outcome would be useful.

As Americans become more health conscious, the question of the effects of exercise, one's overall health, and pregnancy outcome will become increasingly important. Continuation of the author's research in this area is certainly warranted and welcomed.

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Response declined

Normal amniotic pressure in oligohydramnios after preterm rupture of membranes

To the Editors: In their article on amniotic pressure in oligohydramnios (Nicolini U, Fisk NM, Rodeck CH, Talbert DG, Wigglesworth JS. Low amniotic pressure in oligohydramnios—Is this the cause of pulmonary hypoplasia? Am J Obstet Gynecol 1989;161:1098-101), Nicolini et al. propose low amniotic pressure as a possible mechanism contributing to lung hypoplasia in pregnancies complicated by reduced liquor volume. They also state that they have not measured the intraamniotic pressure in cases of oligohydramnios as a result of premature rupture of the membranes.

We have performed pressure measurements in three pregnancies complicated by early rupture of membranes and resultant oligohydramnios with a fluid-filled system and a solid-state pressure transducer. Intraamniotic pressures are zeroed to the top of the maternal abdomen.

The intraamniotic pressures were recorded before and after the infusion of 200 ml of Hartmann's solution into the amniotic cavity to facilitate ultrasonographic visualization of the fetus. In the first case in which liquor was draining for 2 weeks before the procedure at 20 weeks, the intraamniotic pressure was 12 mm Hg. Preterm labor occurred at 29 weeks and a male infant weighing 1425 gm was delivered. He died of respira-

tory failure at 43 days after a stormy neonatal course; autopsy was refused. The other two cases involved preterm rupture of membranes at 21 and 22 weeks, respectively. In the former, intraamniotic pressure was 3 mm Hg. The baby was delivered at 36 weeks and 3 days, and had an uncomplicated postnatal period. The pressures in the last case were 9 mm Hg before and 10 mm Hg after infusion, and this pregnancy resulted in preterm labor at 31 weeks' gestation. The infant died in the neonatal period and autopsy confirmed pulmonary hypoxemia.

According to published data,[1,2] the intramniotic pressures in these cases were within the normal range. Nicolini et al. suggest that the low pressure in oligohydramnios contributes to pulmonary hypoplasia by allowing intrapulmonary fluid to escape from the lungs down a pressure gradient. In these cases with normal intraamniotic pressure, this is unlikely to be a mechanism, particularly in the first case in which the pressure was at the upper limit of normal. Possibly the higher intraamniotic pressure is a factor in the genesis of preterm ruptured membranes. The first infant died of chronic lung disease. This could have been caused by prematurity alone, but the high level of respiratory support required, and the difficulties encountered in ventilating him, were thought to be a result of bronchopulmonary dysplasia.

The mechanism of pulmonary hypoplasia remains unclear, but we have demonstrated that oligohydramnios per se is not always associated with low amniotic pressure. However, oligohydramnios, regardless of cause, is associated with respiratory problems in the neonatal period. Clinicians therefore need to look beyond amniotic pressure for the cause of pulmonary hypoplasia.

Pam Johnson, MBBS, and Darryl J. Maxwell, MBBS

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Reply

To the Editors: We thank Drs. Johnson and Maxwell for their interest in our hypothesis on the pathogenesis of pulmonary hypoplasia. On the basis of three observations, they claim that oligohydramnios is not always associated with low amniotic pressure. This does not surprise us. In our recent series,[1] although all 24 cases of severe oligohydramnios (deepest pool <0.5 cm) had amniotic fluid pressure below the mean for gestational age, 16 were within the reference range. Indeed, our latest observations (unpublished) indicate that amniotic pressure in 37 cases of severe oligohydramnios is approximately 2 SDs lower (mean Z score = −2.04; 95% confidence intervals = −1.64 to −2.44; $p < 0.0001$) than the mean for gestational age in 117 pregnancies with normal amniotic fluid volume. Amniotic pressure in severe oligohydramnios caused by ruptured membranes ($n = 6$) was not as low as in those with intact membranes, but was nevertheless significantly lower than in controls (mean Z score = −1.09, 95% confidence intervals = −0.46 to −1.72; p 0.019).

Unfortunately, Drs. Johnson and Maxwell do not specify their criteria used to define olighydramnios. This is crucial since pressure does not seem to be reduced in cases of mild or moderate oligohydramnios.

Animal studies suggest that the mechanism of pulmonary hypoplasia in oligohydramnios is failure of retention of lung liquid within the developing airways.[2,3] Our observation of low amniotic pressure in oligohydramnios indicates that external compression is an unlikely cause for this loss of lung liquid. Instead we have hypothesized that an increase in the alveolar-amniotic gradient might be responsible.

The correspondents dismiss our hypothesis on the basis of finding "normal" amniotic pressure in a series of three pregnancies with oligohydramnios, without providing any evidence that these fetuses had pulmonary hypoplasia.

The validity of our hypothesis will be more appropriately tested in experimental animal studies currently under way.

Umberto Nicolini, MD, Nicholas M. Fisk, MD, and Charles H. Rodeck, MD

Institute of Obstetrics and Gynecology, Royal Postgraduate Medical School, Queen Charlotte's and Chelsea Hospital, Goldhawk, London, England W6 OXG

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Measurement of cardiac output by impedance technique

To the Editors: Masaki et al. have reported their experience in pregnancy with a new model of the Noninvasive Continuous Cardiac Output Monitor, model 3 (NCCOM-3), a device that measures cardiac output by impedance technique (Masaki DI, Greenspoon JS, Ouzounian JG. Measurement of cardiac output in pregnancy by thoracic electrical bioimpedance and thermodilution. AM J OBSTET GYNECOL 1989;161:680-4). The statistical analysis of the data and the interpretation of their results raise concerns.

The authors state that they used the method of Bland and Altman to assess agreement between methods. Their Fig. 2 is cited as an example of that method. This is a simple plot of one measure against the other, from

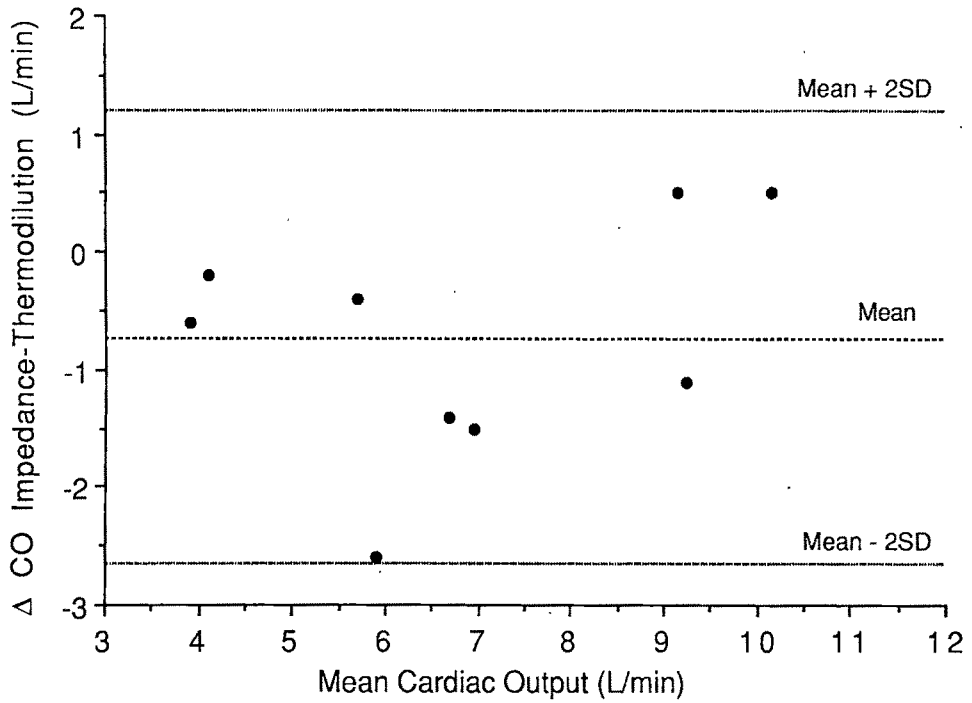


Fig. 1. Plotted data of Masaki et al.

which, according to Bland and Altman, "it will be difficult to assess between-method differences." We could find no other evidence that the Bland-Altman analysis was performed. To use the Bland-Altman method the mean of two measurements is plotted against the difference. Data from the study of Masaki et al. are plotted in Fig. 1. Reference lines of mean difference between measurements and 2 standard deviation confidence intervals have been included for comparison.

This method of analysis reveals two important points. First, impedance underestimates cardiac output in pregnancy. The mean difference in measurements is −0.73 L/min. Second, the confidence intervals are not small. The combination of these weaknesses places the lower confidence limit 2.7 L/min below what would have been obtained by thermodilution.

The discussion of the article fails to recognize the underestimation of cardiac output by impedance. Although the slope of their regression line is 1.04, the intercept is −1.03. Therefore the regression line parallels the line of identity with measurements by impedance being 1 L/min below those by thermodilution. The mean of measurements made by thermodilution is 7.24 ± 2.1. By impedance, the mean is 6.5 ± 2.5. The means are significantly different at $p = 0.05$ (paired t test). This shortcoming of the impedance technique has been previously demonstrated by the study of Atkins et al. in which cardiac output was not found to be elevated throughout most of pregnancy. The sources of potential errors have been reviewed by de Swiet and Talbert.[3] The new edition of the NCCOM-3 does not seem to overcome all of these problems.

The authors also have not discussed the large underestimations of cardiac output in three patients. In patient 4 the cardiac output was underestimated by 19.8%; in patient 5, by 19.1%; and patient 9, by 35.6%. These differences are large enough to be of clinical significance. Two of these patients had severe preeclampsia. We have previously reported similar large underestimations of cardiac output by impedance technique in this population.[4] In the patients we described, the errors in measurement of cardiac output were associated with very low, "subphysiologic," measurements of maximum $(dZ/dt)_{max}$ (the maximum rate of impedance change), one of the parameters in the Sramek-Bernstein equation. This is the same problem that makes measurement of cardiac output in patients with septic shock inaccurate.[5] I suspect that the patients described by Masaki et al. also had a low $(dZ/dt)_{max}$ value. Abnormalities in this parameter may indicate patients in whom measurement of cardiac output by impedance is inappropriate.

Finally, the authors have chosen to remove two patients from the study retrospectively because their medical conditions are ones in which the method does not work well. These determinations must be made prospectively before evaluating the data. Retrospective exclusion of subjects introduces substantial bias into the study.

Measurement of cardiac output by impedance technique in pregnancy must be done with an understanding of the limitations of the technique. First, it underestimates cardiac output in pregnancy. This difference is of importance when nonpregnant and pregnant women are compared. Second, there may be large un-

derestimations in cardiac output of patients with preeclampsia. These errors may provide misleading information about the hemodynamics of the disease and may prompt the physician to make errors in treatment of individual patients. In its present state of development, impedance technique of measuring cardiac output is not reliable in pregnancies complicated by preeclampsia.

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Response declined

Ultrasonography's role in detection of intrauterine synechiae

To the Editors: After reading the article "Intrauterine adhesions: Hysteroscopic diagnosis, classification, treatment, and reproductive outcome" by Valle and Sciarra (Am J Obstet Gynecol 1988;158:1459-70) I performed a level II ultrasonographic examination associated with genetic amniocentesis in a patient at 16 weeks' gestation. She had undergone postmiscarriage dilatation and curettage 10 years ago. Complete amenorrhea was relieved by hysteroscopy at that time. Ultrasonography at the time of genetic amniocentesis showed several uterine synechiae.

That pregnancy prompts me to remark on another patient in whom there had been a history of previous uterine surgery because of myoma. Ultrasonography at 16 weeks' gestation showed a uterine synechia. At 38 weeks' gestation the patient had a persistent breech presentation with the uterine synechia truly tethering the anterior uterine wall to the posterior uterine wall. The synechia was very low in the uterine cavity. Delivery was by elective cesarean section.

My question is to other obstetrician-ultrasonologists involved in ultrasonographic evaluation of the uterus in similar situations of patients who have undergone previous uterine surgery. Have they also seen instances in which uterine synechiae have had significant effects on obstetric management when the synechiae were visualized at the time of an ultrasonographic examination in the second trimester?

Is it reasonable to recommend ultrasonographic evaluation routinely early in the second trimester in patients who have had intrauterine surgery and/or intrauterine adhesion therapy?

John D. Stephens, MD
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Addendum

Regarding concerns about intrauterine "shelves" in pregnancy, see the article from which the following is quoted (Brown DL, Felker RE, Emerson DS. Intrauterine shelves in pregnancy: sonographic observations. Am J Roentgenol 1989;153:821-4). "The patients had a history of dilatation and curettage or cesarean delivery, which predisposes the patient to formation of synechiae. This experience suggests that when a shelf of tissue where the free edge is present within the pregnant uterus, there should be no concern for the development of amniotic band syndrome as long as there is a complete sonographic survey of the fetus which reveals no abnormalities." There are other obstetric management implications above and beyond those regarding fetal development that need to be addressed and that I hope I have outlined here.

Reply

To the Editors: Little experience exists on the use of ultrasound to detect intrauterine adhesions either during pregnancy or in the nonpregnant uterus. With the rapid improvement in ultrasound technology, particularly with vaginal transducers, ultrasonography is being used with increasing frequency to evaluate the uterine cavity, with special interest in the assessment of endometrial thickness during various phases of the menstrual cycle.[1] In addition, leiomyomas, endometrial polyps, and malignant growths with myometrial invasion have been clearly seen.[2] Uterine wall defects related to previous surgery, particularly cesarean section scars, have also been evaluated ultrasonographically.[3]

Although hysterosalpingography and hysteroscopy are the best methods available today to accurately diagnose intrauterine adhesions, ultrasonography has been suggested as a method to detect this condition in nonpregnant women.[4] Because it is noninvasive, ultrasonography is an appealing method of evaluation, particularly in patients who are symptom-free but have a history of postpartum or postabortal curettage or other intrauterine surgery. Thus ultrasonic evaluation may eventually screen those patients likely to benefit from hysterosalpingography or hysteroscopy with precise diagnostic methods also permitting treatment of intrauterine adhesions. However, before ultrasound is used as a screening tool, its sensitivity, specificity, and predictive value should be determined by extensive clinical evaluation.

In the pregnant woman, ultrasonographic examination may become the method of choice to evaluate intrauterine pathology. This approach may be most applicable to patients who attempt pregnancy after lysis of intrauterine adhesions, but who have not had the benefit of a subsequent evaluation by hysterosalpingography or hysteroscopy. As suggested by Dr. Stephens, ultrasonography may be valuable in patients who become pregnant after therapy for extensive moderate to severe intrauterine adhesions, inasmuch as these patients may achieve pregnancy despite residual adhesions. Once pregnancy has been established, treatment of intrauterine adhesions is usually not possible; however, the ultrasonographic detection of adhesions during early pregnancy may serve as a warning to the clinician for closer obstetric surveillance. Further experience must be prospectively accumulated in such patients before ultrasound can be generally recommended.

We appreciate Dr. Stephens' interest in our article and encourage him to continue his ultrasonographic observations on intrauterine adhesions in both the nonpregnant uterus and during pregnancy.

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and John J. Sciarra, MD, PhD

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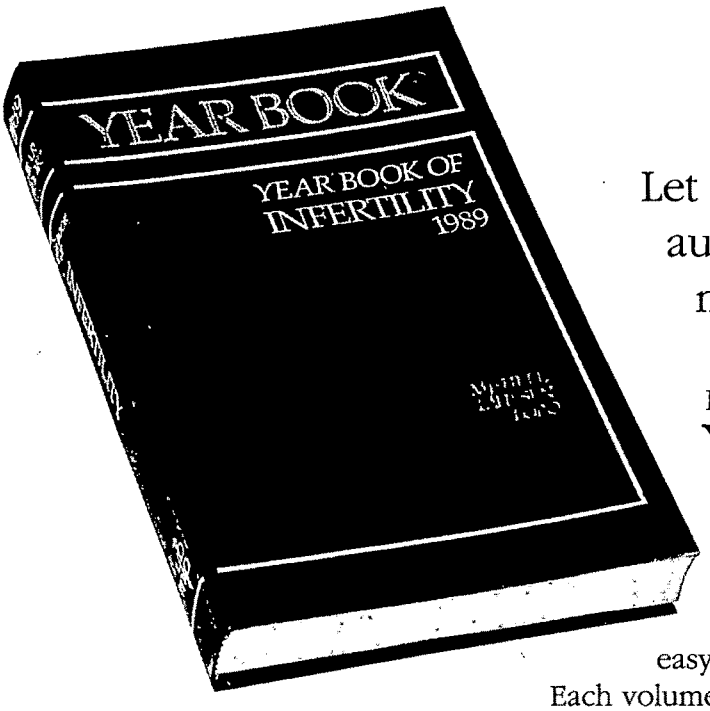
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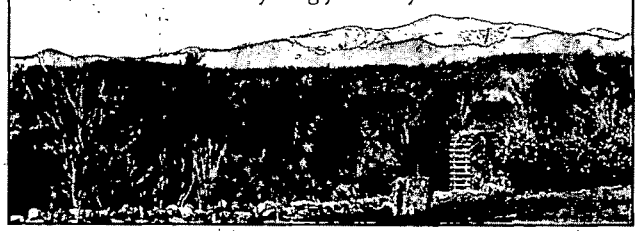
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Connecticut's first and only staff-model HMO seeks board eligible/certified OB/GYN to join group of 6 physicians and 7 midwives in providing full range of obstetrical services to patients throughout our New Haven region. Affiliated with Yale New Haven Hospital and Yale School of Medicine, this practice environment offers the physician interested in developing his/her skills in a manged-care arena the chance to practice community medicine in a supportive setting while remaining within easy reach of New York and Boston metropolitan areas. Competitive salary and benefits package. Send C.V. to: **Robert Scalettar, M.D., Vice President for Clinical Affairs, Community Health Care Plan, 221 Whitney Avenue, New Haven, CT 06511.** We are an Equal Opportunity Employer.

CHCP

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ELKO REGIONAL MEDICAL CENTER

762 - 14th Street Elko, Nevada 89801 (702) 738-3111

OBSTETRICIAN/GYNECOLOGIST

Nevada's oldest multi-specialty clinic seeks BE/BC OB/GYN to join two other OB-GYN's and Nurse Midwife in very busy practice. Lucrative opportunity for full range of specialty practice. All fee for service with excellent collection ratio. Guaranteed salary for six months leading to full partnership. Comprehensive benefit package including malpractice insurance. Elko is a thriving community surrounded by mountains and wilderness areas. Recreation year round. Please send C.V. to:

Cherie Atwood, Administrator
Elko Regional Medical Center
762-14th Street
Elko, Nevada 89801
(702) 738-3111

OB/GYN CHIEF
PACIFIC NORTHWEST

The Department of Obstetrics and Gynecology at Emanuel Hospital and Health Center in Portland, Oregon is currently accepting applications for the position of Chief of Obstetrics and Gynecology. This hospital-based position is in a 554 bed tertiary hospital in the beautiful Pacific Northwest, sixty minutes from the Oregon Coast, Cascade Mountains and Columbia River Gorge. Applicants must be board certified in OB/GYN, have administrative, clinical, teaching, and research experience. For confidential consideration, please send CV to:

William P. Young, M.D., Chief of OB/Gyn
Department of Obstetrics & Gynecology
Emanuel Hospital & Health Center
2801 N. Gantenbein
Portland, OR 97227

BRIGHAM AND WOMEN'S HOSPITAL

Perinatologist

The Brigham and Women's Hospital, a major teaching hospital of Harvard Medical School, seeks a full-time perinatologist to join the Division of Maternal-Fetal Medicine.

Applicants should be board-certified or active candidates for certification in Obstetrics and Gynecology and Maternal-Fetal Medicine.

Academic rank will be commensurate with experience and achievements.

Commitment to clinical care, research, and teaching are essential.

Send inquiry and curriculum vitae to:

Michael F. Greene, M.D.
Director, Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Brigham and Women's Hospital
75 Francis Street, ASB1-3-078
Boston, Massachusetts 02115

The Brigham and Women's Hospital is an affirmative action, equal opportunity employer.

Fargo Clinic
MeritCare

OB-GYN

Large multispecialty group is seeking BC/BE Obstetrician-Gynecologist to join seven member department. Department is active in donor and husband insemination. Opportunity to develop Invitro and Gift Programs available.

Fargo Clinic is a 250 physician group that practices in 30 locations throughout eastern ND and western MN. The main facility is located next to St. Luke's Hospitals, a 400 bed tertiary care & trauma center. St. Luke's is a NACHRI designated Children's Hospital with a level III ICN.

Fargo-Moorhead is a tri-college community of 130,000 located just minutes from the lake country of western Minnesota. Abundant cultural, recreational, sporting and hunting activities available year around.

Outstanding compensatory package available. Respond to Robert C. Montgomery, M.D., Chairman, Physician Recruitment, 737 Broadway, Fargo, ND 58123.

Life.

It's our life's work.

If your mission in life is to practice the ideals of medicine without administrative demands, we invite your inquiry.

Group Health Plan in St. Louis is a staff model HMO that promotes the ideals of private practice while freeing doctors from the financial baggage of the private practitioner.

Group Health Plan isn't for every physician. Just for those few who want to practice medicine without compromise.

For an interview please talk with the Medical Recruiter at (314) 993-5955. Or write Group Health Plan, 11475 Olde Cabin Road, St. Louis, Mo. 63141. An equal opportunity employer.

GROUP HEALTH PLAN

Two person OB-GYN group, well established, in prestigious Long Island community. Looking for BC/BE Associate leading toward partnership. University and Community hospital affiliations, in-office sonography, cryo surgery, and colposcopy. Excellent salary, benefits, and future.

Send C.V. to:
Marc Harvey, M.D., F.A.C.O.G.
100 Manetto Hill Road
Suite 306
Plainview, NY 11803

Chairperson

Obstetrics and Gynecology

Leadership position at a major teaching hospital in Northern New Jersey affiliated with the School of Graduate Medical Education of Seton Hall University. The Department has a fully approved residency program and a wide range of tertiary clinical services. Please forward applications and nominations to Barry Weiner, M.D., Jersey City Medical Center, 50 Baldwin Avenue, Jersey City, NJ 07304. An Equal Opportunity Employer.

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ATLANTA, GEORGIA

Board Certified/Board Eligible OB/GYN for excellent opportunity in rapidly growing practice. Single-specialty group works separately, but within large multi-specialty group. Physicians work out of just one office and one hospital. 1 in 6 call/coverage. $110,000 and $120,000 salary plus performance bonus. All expenses and benefits included. Position offers quality lifestyle. Send CV or call Shane Hunt or Brad Peters, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 AJOGO, Atlanta, GA 30346, Tel. 1-800-544-1987.

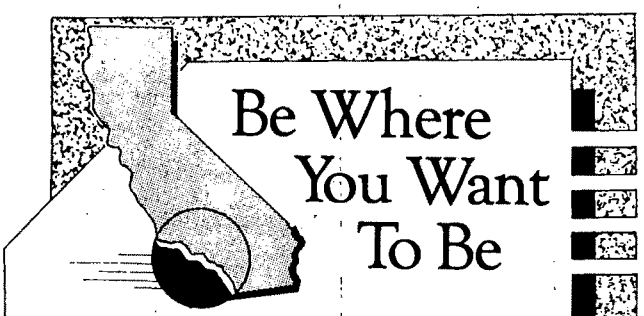
SUPERIOR PRACTICE OPPORTUNITY FOR A GYNECOLOGIST IN BEAUTIFUL, HISTORIC, CHARLESTON, SOUTH CAROLINA

A unique practice opportunity is available for a board certified GYNECOLOGIST to share office space with a well established, progressive (board certified) GYNECOLOGIC ONCOLOGIST.

- Well located, attractive office with common waiting room and business space with six (6) examining rooms and two physician's offices.
- Pleasant professional atmosphere.
- Shared on-call coverage available.
- Close proximity to two (2) JCAH accredited hospitals and Medical University.
- Located in Charleston, S.C., enjoy the cultural and recreational amenities of a cosmopolitan lifestyle, complimented by affordable housing, outstanding educational facilities, and a year round temperate climate.
- Near Kiawah, Seabrook, and Hilton Head Island Resorts.
- S.C. Malpractice rates lower than other areas.

To learn more about this unique practice opportunity, please call or forward your curriculum vitae to:

Myron Lutz, M.D.
1606 Ashley River Road
Charleston, S.C. 29407
803/556-4380



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At **Southern California Permanente Medical Group (SCPMG),** you can be exactly where you want to be — in terms of your professional practice and in terms of lifestyle.

We are a physician-managed, multi-specialty medical group serving the nation's largest healthcare organization.

Our continued growth has created new opportunities for **Obstetricians/Gynecologists** to join one of our Obstetric practices. To qualify you must be Board Certified/Eligible and proficient in modern techniques. University affiliation and research is encouraged.

You'll have a choice of professional environments ranging from a 250-bed community hospital to a major teaching facility in a number of prime Southern California locations.

We offer • **Paid Malpractice Insurance** • **Predictable Hours** • **Guaranteed Practice and Income.**

For more information, call: **(800) 541-7946**

Or send your curriculum vitae to:

Irwin P. Goldstein, M.D.
Associate Medical Director
SCPMG, Dept. 006
Walnut Center, Pasadena, CA 91188-8013

KAISER PERMANENTE
Southern California Permanente Medical Group

OBSTETRICS & GYNECOLOGY

Group Practice Opportunity: A six practitioner group (4 MDs, 2 male and 2 female, and 2 NPs) seeks a new board eligible/board certified associate. Located in the five college community of Amherst, Smith, Mt. Holyoke and Hampshire Colleges and the University of Massachusetts. We have a modern office with NST and ultrasound, adjacent to a 250 bed community hospital, with laser facilities and epidural anesthesia coverage. This is a wonderful practice opportunity in a beautiful location. Please contact: Gina Tucker, Office Manager, 61 Locust Street, Northampton, MA 01060, (413) 584-2303.

OBSTETRICS/ GYNECOLOGY

29 physician multispecialty group with two BC OB/GYN physicians is looking to add a third BC/BE physician. Bemidji Clinic—MeritCare is located in a college community of 15,000 surrounded by lakes and tress. Bountiful hunting, fishing, and outdoor recreational opportunities. North Country Hospital is a modern 89 bed hospital; Approximately 1000 births a year; 4 surgery suites; and 15 bed nursery.

Bemidji Clinic is affiliated with a 250 physician multispecialty group located in Fargo, ND and affiliated with a 400 bed level II hospital with a 24 level III Intensive Care Nursery.

Excellent compensation and benefit package with incentive pay plan. To discuss this exceptional opportunity further please contact C. C. Lowery, Administrator, Bemidji Clinic, 1233 34th St. NW, Bemidji, MN 56601 or call 1-218-751-1280.

Join us.

PACIFIC NORTHWEST

GROUP HEALTH COOPERATIVE OF PUGET SOUND, a 375,000-member prepaid group practice, currently has a position available for an Obstetrician/Gynecologist. We are a multi-specialty organization located in the scenic Seattle area.

To inquire, write to:
Manager, Medical Staff Personnel
Group Health Cooperative
of Puget Sound
521 Wall Street
Seattle, WA 98121

Group Health Cooperative
of Puget Sound
Affirmative Action/Equal Opportunity Employer

OB/GYN
Northeastern Wisconsin

18 physician multi-specialty group located in a medium-sized Lake Michigan community seeks a second and third BC/BE physician to join its department of Obstetrics and Gynecology. Positions offer an excellent professional, financial and life-style opportunity. Send C.V. or call James Robinson, Administrator, Manitowoc Clinic, 601 Reed Avenue, Manitowoc, WI 54220. Telephone: (414) 682-8841.

Obstetrics/ Gynecology

WISCONSIN: Marshfield Clinic, a multi-specialty group practice with 350 physicians is seeking BE/BC obstetricians/gynecologists to join expanding (40-50 physician) regional centers in Chippewa Falls and Woodruff, Wisconsin. A third OB/GYN is needed for each facility. Chippewa Falls is located 1 1/2 hours from downtown Minneapolis/St. Paul and twenty minutes from a major four year campus of the University of Wisconsin. Known as the "Lakeland Area" (over 1,000 navigable lakes) Woodruff is truly one of the most attractive vacation areas in the upper Midwest and renown for its year-round outdoor recreational activities. Both communities offer exceptional recreational, cultural, and educational opportunities. An emphasis on quality practice and life-style is combined with a total compensation package on reaching membership in excess of $200,000. Starting salary negotiable. Fringe benefit package outstanding; includes self-insured malpractice. No start-up expense. Send C.V. and references to:

David L. Draves
Director, Regional Development

1000 North Oak Avenue
Marshfield, Wisconsin 54449
or call collect at
(715)387-5376

Marshfield Clinic

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
MEDICAL COLLEGE OF GEORGIA

TWO MATERNAL-FETAL MEDICINE FACULTY TENURE TRACK POSITIONS AVAILABLE

—Duties: patient care – teaching – research.
—Qualifications: OB/GYN board certified and specialty board certified or pending.
—Rank and Salary: Open based on experience.

The Obstetrics and Gynecology Department at the Medical College of Georgia provides support and opportunity for academic advancement and professional growth. Located in Augusta, Georgia a progressive community offering a pleasant climate with an environment for quality family living. Area population 375,000.

Address inquiries with Curriculum vitae to: Donald M. Sherline, MD, Chairman, Department of Obstetrics and Gynecology, CK170, Medical College of Georgia, Augusta, Ga. 30912.

Equal Opportunity/Affirmative Action Employer

Director, Reproductive Endocrinology and Infertility Medical University of South Carolina

Board certified Reproductive Endocrinologist is being recruited to assume the directorship of this division. This individual will be responsible for the administration as well as teaching, clinical and research activities of this division in an academic setting.

Academic rank and salary will be commensurate with experience and achievements.

Qualified interested applicants are invited to submit a curriculum vitae to:

William T. Creasman, M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
Medical University of South Carolina
171 Ashley Avenue
Charleston, SC 29425

MUS is an affirmative action, equal opportunity employer.

OBSTETRICIAN/ GYNECOLOGISTS

Group Health Association, one of Washington, DC's most respected names in the health maintenance field, has immediate and future openings for board certified or eligible Obstetrician/ Gynecologists.

Consisting of nine multi-specialty medical centers and 200 physicians, Group Health's highly skilled support staff serves over 150,000 members. This staff attends to the details of clinical administration, allowing you the freedom to devote your energy to practicing medicine. Further, GHA's challenging work environment offers a diverse patient population and affiliation with the area's finest hospitals.

A generous benefits package including vacation, sick leave and insurance coverage (malpractice, life, retirement, disability and dental) awaits you in return for your expertise. In addition, you can look forward to company-paid hospital and licensing fees, professional society dues, continuing education as well as predictable office hours.

If you would like more information, please send your CV. to the address below or call Mary Hines, Physician Recruiter, on 1-800-336-1442 or in DC Metro area, (202) 364-7442.

Turner Bledsoe, M.D., Medical Director

Group Health Association
4301 Connecticut Avenue, N.W.
Washington, D.C. 20008

An Equal Opportunity Employer

Obstetrics/Gynecology, Laurel, MS—Join two-physician association. 1 in 3 call/coverage. Search sponsored by 275-bed hospital. Community of 30,000 just 90 minutes from Gulf Coast and 60 minutes from Jackson, MS. Excellent financial package. Paid interviewing and relocation expenses. Send CV or call Gregory Pilgrim, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 AJOGO, Atlanta, GA 30346, Telephone: 1-800-544-1987.

OBSTETRICS/GYNECOLOGY

Here's a practice opportunity we believe you would enjoy. Six family physicians, two surgeons, an optometrist and a clinical psychologist in a busy practice in sister cities on the Red River in southern North Dakota/western Minnesota. The clinic facility is new with ample room for additional staff. Hospital is a modern 95 bed hospital with over 360 deliveries a year. Two of the physicians on staff are currently doing C-sections.

Wahpeton/Breckenridge has a combined population of 15,000 with a patient draw area of over 40,000. Wahpeton is the home of the ND State College of Science and each community has public and parochial primary education.

Will join a 250 physician multispecialty group affiliated with a 400 bed level II hospital which has a NACHRI designated Children's Hospital and a 24 bed level III ICN.

For further information regarding this excellent practice opportunity please contact Robert Ostmo, M.D., 227 6th St. N., Breckenridge, MN 56520 or call 1-218-643-7813.

OBSTETRICIAN GYNECOLOGIST

Western Massachusetts staff model Health Maintenance Organization is seeking two full-time, Board Certified/Board Eligible Obstetrician/Gynecologists to join our expert staff of five physicians and five midwives.

Our multi-specialty group practice employs 70 full-time physicians and provides care for a membership of over 65,000 patients in our modern suburban facilities. Inpatient care is provided at a 900-bed Tufts affiliated teaching hospital.

Attractive Pioneer Valley location with fine educational, cultural and recreational opportunities. Excellent salary and comprehensive benefit program. Please send curriculum vitae to: Oded Rencus, M.D., Chief of OB/GYN, 305 Bicentennial Highway, Springfield, MA 01118 or call (413) 594-3111.

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KAISER PERMANENTE

OBSTETRICIAN-GYNECOLOGIST

The Permanente Medical Group, Inc., of San Jose, California is looking for BC/BE physicians for immediate openings in the OB/GYN Department. Positions available either at the main facility in San Jose, or at satellite medical offices in Gilroy. The young, dynamic, department is still growing and currently has seventeen physicians and two nurse practitioners. Our outstanding benefits package includes full coverage malpractice insurance. San Jose and Gilroy share excellent access to Bay Area cultural and recreational activities.

Recent salary advances allow extremely competitive compensation starting with the first year of employment.

For more information, please contact:

Jerome L. Nehemiah, M.D.
Chief, Department of Ob/Gyn
The Permanente Medical Group, Inc.
260 International Circle
San Jose, CA 95119
or telephone: 408-972-6180 (collect)

MRHP

The **Michael Reese Health Plan,** a large well-established HMO serving its members in 20 Health Centers throughout the Chicago Metro area, is seeking additional Board Certified/Eligible physicians in

Obstetrics Gynecology

Physicians with the Health Plan enjoy a full practice with modern facilities and equipment as well as opportunities for teaching. All specialty facilities available.

A highly-competitive salary and excellent benefits complement a rewarding practice and lifestyle.

Interested applicants should address inquiries to:

Alfred Kendrick, M.D.
Medical Affairs
MICHAEL REESE HEALTH PLAN
2545 King Drive, Chicago 60616
or call (312) 808-4551

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Finger Lakes Region
Ithaca, New York

Unique opportunity for patient oriented physician in comprehensive OB-GYN service, building on established patient base of 6,000 patients. To include out-patient gynecology, obstetrics, surgery, infertility, and abortions. First call protection from nurse-midwives. Progressive university community (home of Cornell University) offers cultural attractions of a city with the benefits of small town living. Competitive salary, excellent benefits including malpractice. Summer/Fall 1991.

Send CV To: Joyce Leslie, M.D., Planned Parenthood of Tompkins County, 314 W. State St., Ithaca, NY 14850.

Planned Parenthood®
of Tompkins County

PERINATOLOGIST

The Reading Hospital and Medical Center, a 625-bed teaching hospital with 2,400 deliveries per year, is seeking a Perinatologist to augment current genetics and perinatal service. With a 24-hour in-house obstetrical anesthesiology team and neonatology coverage, the Perinatologist would be Director of the Perinatal Service.

Responsibilities include residency teaching, supervision of antenatal testing unit, and consultations with private practitioners and some private practice. Close association with a University service for administrative and educational backup, coverage, and research involvement.

We offer a competitive salary with a comprehensive flexibly structured benefits package. Located in a desirable growth area in East Central PA, The Reading Hospital and Medical Center is a recognized leader in the delivery of health care and health care education. The community is an excellent place to raise a family with superb schools and varied recreational/cultural opportunities. The nearby metropolitan areas of New York City, Philadelphia and Baltimore/Washington, DC offer additional advantages. Interested candidates please submit curriculum vitae to:

Peter Schwartz, M.D.
Chairman, OB/GYN

THE READING HOSPITAL and MEDICAL CENTER

Reading, PA 19603

Equal Opportunity Employer m/f/h/v



NORTHERN CALIFORNIA

The Permanente Medical Group, a growing multispecialty group, is recruiting for positions in our beautiful Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley.

REPRODUCTIVE ENDOCRINOLOGIST

• SAN JOSE •

We are currently seeking a Reproductive Endocrinologist to establish and run a reproductive endocrinology subdivision in the department. Duties would include the full spectrum of reproductive endocrinology, outpatient and surgical management of infertility. Fellowship certification would be preferred. The department currently has 17 physicians and is still growing. We offer a generous benefits package including full coverage malpractice insurance. San Jose has beautiful weather and excellent access to Bay Area recreational and cultural activities.

For more information, please contact: Jerome L. Nehemiah, M.D., Chief, Department of OB/GYN, The Permanente Medical Group, Inc., 260 International Circle, Dept. AJOBG, San Jose, CA 95119, or call collect (408) 972-6180. EOE

KAISER PERMANENTE

Good People. Good Medicine.

OB/GYN WISCONSIN

Multi-specialty group in suburban Milwaukee seeks BC/BE Obstetrician/Gynecologist to join 6 physician OB/GYN department. Single site, single hospital practice. Competitive salary and fringe benefits. Forward inquiries and CV to:

Administrator
P.O. Box 427
Menomonee Falls, WI
53051

OBSTETRICIAN/ GYNECOLOGIST

Immediate opening for a Board Certified/Eligible physician to work with 5 others at a well-established, growing HMO. Rochester Medical Group is a multispecialty medical group practice serving 45,000 patients at multiple sites. Clinical faculty appointment at the University of Rochester is available with this position. Competitive salary/benefits with opportunities for research and resident teaching. Send resume to:

Patricia Hosking
Rochester Medical Group, PC
1800 Hudson Avenue
Rochester, NY 14617

University of California, Irvine, College of Medicine, OB/GYN. Assistant Professor-In-Residence (M.D.), board eligible/certified in Obstetrics and Gynecology with subspecialty training in Gynecologic Urology with extensive pelvic surgery experience. Strong research focus in genuine stress incontinence. Duties include functioning as Director of Ambulatory Care Service; medical student, resident, and postgraduate teaching; clinical service supervision; clinical and laboratory research.

UCI is an Equal Opportunity/Affirmative Action Employer.

Send C. V. and five references to

Thomas J. Garite, M.D.
Obstetrics and Gynecology
UCI Medical Center
101 The City Drive
Orange, CA 92668

OB-GYN FACULTY IN JAPAN

Ideal for Sabbatical

Univ. of Hawaii Medical Education Program in Okinawa, Japan invites applications for faculties in Ob-Gyn (General, Perinatology, or Oncology) for a period of 3-6 months (between July '91 until June '93). Salary commensurate with experience plus 30% overseas allowance, airfare, furnished accommodation with all utilities paid. Additional allowance of approximately Yen 120,000 per month.

Applications with C.V. to:

Y.B. Talwalkar, M.D., Program Director
University of Hawaii Program
Okinawa Chubu Hospital,
Gushikawa City
Okinawa, Japan 904-22
Serious inquiries call collect
Tel. No.: 09897-3-1515

THE UNIVERSITY OF CHICAGO

GYNECOLOGIST

Full-time Faculty Positions available for Board Certified/Eligible General Gynecologists, Pediatnc Gynecologists and Uro-Gynecologists at The University of Chicago. This is an opportunity to pursue both an academic and clinical career. If interested, send curriculum vitae and list of references to:

ARTHUR L. HERBST, M.D.
Department of Obstetrics and Gynecology

THE UNIVERSITY OF CHICAGO
5841 S. Maryland Ave./Box 446
Chicago, IL 60637

The University of Chicago is an Affirmative Action Equal Opportunity Employer.

The Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine and Hospital, announces the availability of faculty positions in the following areas:

Assistant Professor
General Obstetrics and Gynecology
Maternal-Fetal Medicine

Research and teaching commitment essential. Applicants should be board certified or active candidates for certification in General Ob/Gyn and subspecialty of Maternal-Fetal Medicine.

We are an affirmative action/equal opportunity employer. Minorities and women are encouraged to apply.

Address inquiries to:

Michael T. Mennuti, M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104-4283

THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
UNIVERSITY OF WISCONSIN MEDICAL SCHOOL
MILWAUKEE CLINICAL CAMPUS

is seeking applicants for four (4) full-time faculty positions to participate in the development of a new women's health center and academic program.

Sinai Samaritan Medical Center is in the process of consolidating its obstetrical and gynecological services in a redesigned facility in downtown Milwaukee. The department supports a residency program, the largest perinatal service in Wisconsin (5200 deliveries), consultative ultrasound, genetic and infectious disease programs, and reproductive/endocrine services (including an IVF program). The department is affiliated with Planned Parenthood of Wisconsin.

Qualifications include board candidacy or certification in obstetrics and gynecology and a commitment to teaching residents, medical students, and clinical research. Qualifications for the four positions for GENERAL OB/GYN can take into consideration special individual interests. Special expertise of interest for the department are:

— STATEWIDE FAMILY PLANNING AND AMBULATORY CARE (Part time medical director, Planned Parenthood)
— OPERATIVE LAPAROSCOPY, HYSTEROSCOPY
— UROGYNECOLOGY
— RESIDENT/MEDICAL STUDENT EDUCATION
— OB/GYN ULTRASOUND

Private practice opportunities are also available in an associated offsite multispecialty clinic and all facity members participate in a group practice at the location.

Contact: Fredrik F. Broekhuizen, M.D.
Chairman and Chief
Department of Obstetrics and Gynecology
University of Wisconsin Medical School
Sinai Samaritan Medical Center
Mount Sinai Campus
950 North 12th Street, G405
Milwaukee, WI 53233
(414) 283-7931

OB-GYN

BC/BE OB-GYN sought for full service, 260-bed community hospital in San Francisco's dynamic South of Market area.

- Excellent opportunity to join busy, growing practice.
- Competitive salary and benefits package.

ST. LUKE'S HOSPITAL

Send C.V. to:

Walter Kopp
St. Luke's Hospital
3555 Army Street
San Francisco, CA 94110
(415) 641-6543

State University of New York
Health Science Center
Syracuse

PELVIC SURGERY FELLOWSHIP

The Department of Obstetrics and Gynecology of S.U.N.Y., Health Science Center at Syracuse is offering a one-year fellowship in Pelvic Surgery for qualified candidates.

The Fellowship will include comprehensive training in benign and malignant pelvic surgery, infertility surgery, laser surgery (abdominal, endoscopic and external genitalia), female urology and endoscopy (laparoscopy, hysteroscopy and colposcopy). The program is designed to provide clinical experience and expertise in gynecologic surgery. Research opportunities are available.

Positions are available beginning July 1, 1991.

Qualifications include ABOG eligible/certified status and eligibility for full NY State licensure.

Requests for applications can be sent to:

Michael S. Baggish, M.D.
Professor and Chairman
Department of OB/GYN
S.U.N.Y., Health Science Center
736 Irving Avenue
Suite 308 West Tower
Syracuse, NY 13210

SUNY, Health Science Center is an AA/EEO Employer

Medical Endocrinologist/ Andrologist

Temple University's Department of OB/GYN is seeking applicants for a full-time faculty position in the Section of Reproductive Endocrinology. This position will be a part of a newly established clinical endocrinology-infertility program. The incumbent will develop a clinical andrology research program in male reproductive physiology and infertility.

Candidates should be Board certified or Board eligible in Medical Endocrinology. Salary and academic rank commensurate with experience. Submit C.V. to: **M. Terry Grody, M.D., Acting Chairman, OB/GYN, Temple University Health Science Center, Broad and Ontario Streets, Philadelphia, PA 19140.**

Choose

TEMPLE UNIVERSITY

Gynecologic Oncologist
Philadelphia, Pennsylvania

Progressive, rapidly expanding Division of Gynecologic Oncology located in Center City has full-time academic position available. Candidates must be Board Eligible/Certified gynecologic oncologists. Recruitment at Assistant/Associate Professor level. Excellent clinical and research opportunities available. Competitive salary and benefits program.

Interested persons send curriculum vitae to:

John A. Carlson, Jr., M.D.
Director, Division of
Gynecologic Oncology
Thomas Jefferson University
School of Medicine
Department of Obstetrics
and Gynecology
1025 Walnut Street
Medical College Building-Room 310
Philadelphia, PA 19107

CHAIRPERSON
DEPARTMENT OF OBSTETRICS & GYNECOLOGY

The College of Medicine of the University of Arkansas for Medical Sciences is conducting a search for the position of Professor and Chair, Department of Obstetrics & Gynecology. The Department has active clinical divisions of Maternal-Fetal Medicine, Reproductive Endocrinology, and Gynecologic Oncology. Its research component includes three Ph.D. scientists with expertise in biochemistry, molecular biology, and virology. The candidate must possess sound academic credentials and have shown a committment to patient care, education, and administration. Applications and nominations, including a curriculum vitae, should be sent by November 1, 1990 to: Ernest J. Ferris, M.D., Chair, Search Committee for Chair of Ob/Gyn, U.A.M.S., Mail slot #556, 4301 W. Markham, Little Rock, AR 72205.

The University of Arkansas is an Equal Opportunity/Affirmative Action Employer.

THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY UNIVERSITY OF WISCONSIN MEDICAL SCHOOL MILWAUKEE CLINICAL CAMPUS

is seeking applicants for two (2) additional full-time faculty positions in MATERNAL FETAL MEDICINE to participate in the development of a new women's health center and academic program. The current faculty includes two perinatologists.

Sinai Samaritan Medical Center is in the process of consolidating its obstetrical and gynecological services in a redesigned facility in downtown Milwaukee. The department has the largest perinatal service in Wisconsin (5200 deliveries), has a dedicated antenatal testing and perinatal ultrasonography (including doppler) unit, and is preparing for an expansion in prenatal diagnostic services (including CVS). The department has a midwifery service and an adolescent pregnancy service. The department has an urban care mission while ready to expand into an up-to-date tertiary care perinatal referral center for Southeastern Wisconsin.

Qualifications include board candidacy or certification in maternal-fetal medicine and a commitment to teaching residents, medical students, and clinical research.

Contact: Fredrik F. Broekhuizen, M.D.
Chairman and Chief
Department of Obstetrics and Gynecology
University of Wisconsin Medical School
Milwaukee Clinical Campus
Sinai Samaritan Medical Center
950 North 12th Street, G405
Milwaukee, WI 53233
(414) 283-7931

OB-GYN Physician
Western Massachusetts
("The Heart of the Berkshires")

BC/BE OB-GYN physician to join thriving 4 physician OB-GYN practice that is part of a 55-physician multi-specialty medical P.C. group. Excellent salary, comprehensive benefits, full malpractice coverage, on call schedule every fourth night, early opportunity to become shareholder. Affiliation is with a modern teaching hospital. Area offerings: beautiful recreational area; cultural activities include arts/theater (Tanglewood); located near VT, NY, CT borders. Send CV to:

Berkshire Physicians & Surgeons, P.C.
44 Charles Street
P.O. Box 4759
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WARNINGS

rette smoking increases the risk of serious cardiovascular side effects from oral contracepuse. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and uite marked in women over 35 years of age. Women who use oral contraceptives should be ngly advised not to smoke.

of oral contraceptives is associated with increased risks of several serious conditions including f infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the ous morbidity or mortality is very small in healthy women without underlying risk factors. The idity and mortality increases significantly in the presence of other underlying risk factors such sion, hyperlipidemias, obesity and diabetes. Practitioners prescribing oral contraceptives miliar with the following information relating to these risks. The information contained in this ry is principally based on studies carried out in patients who used oral contraceptives with ulations of estrogens and progestogens than those in common use today. The effect of long f the oral contraceptives with lower formulations of both estrogens and progestogens remains ermined. Throughout this brief summary epidemiological studies reported are of two types: ective or case control studies and prospective or cohort studies. Case control studies provide a re of the relative risk of a disease, namely a *ratio* of the incidence of a disease among oral contrae users to that among nonusers. The relative risk does not provide information on the actual clinical ence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in cidence of disease between oral contraceptive users and nonusers. The attributable risk does proformation about the actual occurrence of a disease in the population. For further information, the is referred to a text on epidemiological methods. 1. THROMBOEMBOLIC DISORDERS AND OTHER LAR PROBLEMS. a. Myocardial Infarction. An increased risk of myocardial infarction has been iated with oral contraceptive use. This risk is primarily in smokers or women with other underlying ictors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and tes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two . The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has shown to contribute substantially to the incidence of myocardial infarctions in women in their hirties or older with smoking accounting for the majority of excess cases. Mortality rates associated circulatory disease have been shown to increase substantially in smokers, especially in those 35 . of age and older among women who use oral contraceptives. Oral contraceptives may compound the ts of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In cular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase d pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been iated with an increased risk of heart disease. Oral contraceptives must be used with caution in ne with cardiovascular disease risk factors. b. Thromboembolism. An increased risk of thromboemic and thrombotic disease associated with the use of oral contraceptives is well established. Case studies have found the relative risk of users compared to non-users to be 3 for the first episode of icial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for n with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the lative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in relative risk of post-operative boembolic complications has been reported with the use of oral contraceptives. The relative risk of s thrombosis in women who have predisposing conditions is twice that of women without such al conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and ng and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed. c. Cerebrovascular diseases. Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events mbotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), pertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users, for both types of strokes, and smoking interacted to increase the risk of stroke. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonrs who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for rs who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hyperon. The attributable risk is also greater in older women. d. Dose-related risk of vascular disease from ontraceptives. A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estroncrease HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved n doses of estrogen and progestogen and the activity of the progestogen used in the contraceptive. vity and amount of both hormones should be considered in the choice of an oral contraceptive. ing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For particular estrogen/progestogen combination, the dosage regimen prescribed should be one which ains the least amount of estrogen and progestogen that is compatible with a low failure rate and the of the individual patient. New acceptors of oral contraceptive agents should be started on preparas containing 0.035 mg or less of estrogen. e. Persistence of risk of vascular disease. There are two s which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a in the United States, the risk of developing myocardial infarction after discontinuing oral contracepersists for at least 9 years for women 40-49 years who had used oral contraceptives for five or e years, but this increased risk was not demonstrated in other age groups. In another study in Great the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation contraceptives, although excess risk was very small. However, both studies were performed with ntraceptive formulations containing 50 micrograms or higher of estrogens. 2. ESTIMATES OF LITY FROM CONTRACEPTIVE USE. One study gathered data from a variety of sources which have ed the mortality rate associated with different methods of contraception at different ages. These s include the combined risk of death associated with contraceptive methods plus the risk attribupregnancy in the event of method failure. Each method of contraception has its specific benefits s. The study concluded that with the exception of oral contraceptive users 35 and older who smoke nd older who do not smoke, mortality associated with all methods of birth control is low and at associated with childbirth. However, smokers 35 and older and non-smokers 40 and older who contraceptives have a significant increase in mortality higher than those using other methods of ntrol. These facts must be weighed in conjunction with failure rates for other methods and the risk ed with subsequent pregnancy. 3. CARCINOMA OF THE REPRODUCTIVE ORGANS. Numerous ological studies have been performed on the incidence of breast, endometrial, ovarian and cervical n women using oral contraceptives. While there are conflicting reports most studies suggest that oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. studies have reported an increased relative risk of developing breast cancer, particularly at a er age. This increased relative risk appears to be related to duration of use. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. 4. HEPATIC NEOPLASIA. Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. 5. OCULAR LESIONS. There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately. 6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY. Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out. 7. GALLBLADDER DISEASE. Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens. 8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users. This effect has been shown to be directly related to estrogen dose. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives. A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users. 9. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with extended duration of use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity. Women with a history of hypertension or hypertension-related diseases, or renal disease, should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users. 10. HEADACHE. The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause. 11. BLEEDING IRREGULARITIES. Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent. 12. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. **PRECAUTIONS:** 1. PHYSICAL EXAMINATION AND FOLLOW UP. A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. 2. LIPID DISORDERS. Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. 3. LIVER FUNCTION. If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function. 4. FLUID RETENTION. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. 5. EMOTIONAL DISORDERS. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 6. CONTACT LENSES. Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. 7. DRUG INTERACTIONS. Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines. 8. INTERACTIONS WITH LABORATORY TESTS. Certain endocrine and liver function tests and blood components may be affected by oral contraceptives: a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radio-immunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. c. Other binding proteins may be elevated in serum. d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids, however free or biologically active levels remain unchanged. e. Triglycerides may be increased. f. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives. 9. CARCINOGENESIS. See WARNINGS section. 10. PREGNANCY. Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections. 11. NURSING MOTHERS. Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child. **INFORMATION FOR THE PATIENT: See Patient Package Insert. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section). Thrombophlebitis and venous thrombosis with or without embolism. Arterial thromboembolism. Pulmonary embolism. Myocardial infarction. Cerebral hemorrhage. Cerebral thrombosis. Hypertension. Gallbladder disease. Hepatic adenomas or benign liver tumors. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea. Vomiting. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Amenorrhea. Temporary infertility after discontinuation of treatment. Edema. Melasma which may persist. Breast changes: tenderness, enlargement, secretion. Change in weight (increase or decrease). Change in cervical erosion and secretion. Diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome. Cataracts. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. Hemolytic uremic syndrome. Acne. Changes in libido. Colitis. **OVERDOSAGE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

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†Serious as well as minor side effects have been reported with the use of oral contraceptives. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate.
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OJ-709R
Low breakthrough bleeding†
Low-impact norethindrone—no significant change in mean values for total cholesterol, HDL, and LDL
For OC patients of all ages
21- and 28-day regin